RAPID-ACTING ANTIDEPRESSANTS: SHARED NEUROPHARMACOLOGICAL MECHANISMS

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ACADEMIC DISSERTATION

To be presented for public examination with the permission of Faculty of Pharmacy of the University of Helsinki, in Lecture Hall 2041, Biocenter 2, Viikinkaari 5, on the 3rd of May, 2019 at 12 o'clock.

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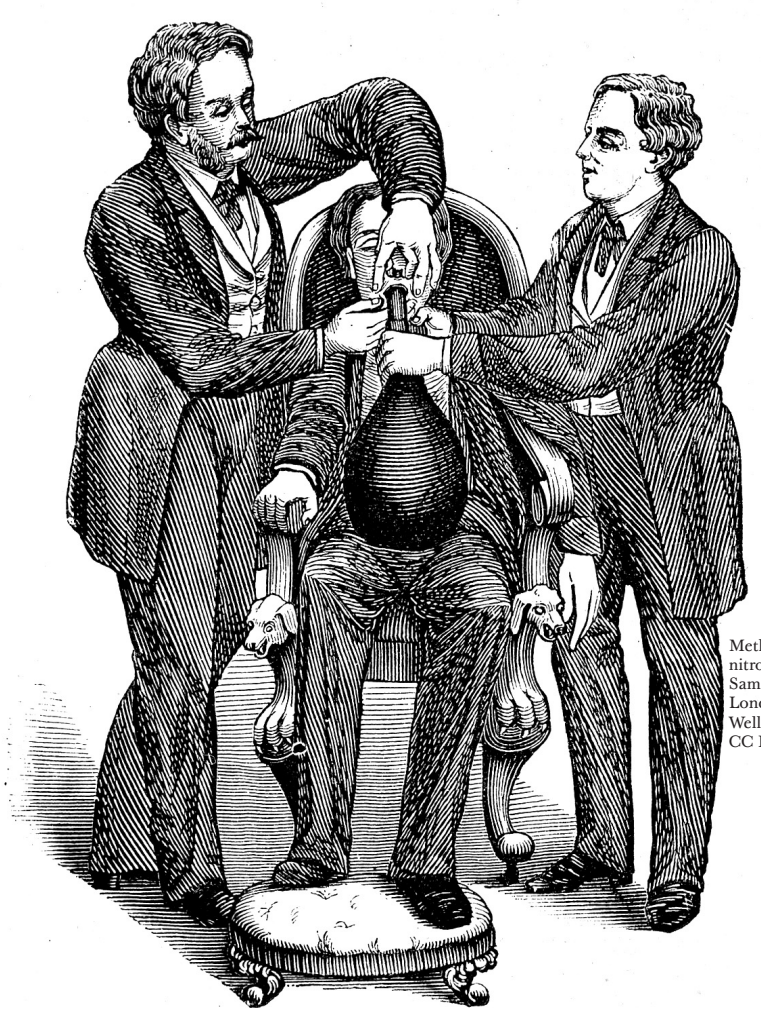
ISBN 978-951-51-5159-9 (print)
ISBN 978-951-51-5160-5 (PDF)

Helsinki, Finland 2019
Press: SidontaPlus Oy



Method of administering nitrous oxide used by Samuel lee Rymer in London, 1863. Credit: Wellcome Collection. CC BY

"There are no differences
but differences of degree
between different degrees of difference
and no difference"

William James

Under the effects of nitrous oxide (1882)

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List of abbreviations

5-HT	5-hydroxytryptamine; serotonin
ACTH	Adrenocorticotropic hormone
Akt	Protein kinase B
AMP	Adenosine monophosphate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor
BF	Bifrontal
BP	Brief pulse
BPRS	Brief Psychiatric Rating Scale
BT	Bitemporal; bilateral
CADSS	Clinician Administered Dissociative States Scale
CaMKIV	Calcium/calmodulin dependent protein kinase IV
CaMKK	Calcium/calmodulin dependent protein kinase kinase
CEN	Central executive network
CMR_{glu}	Cerebral metabolic rate of glucose utilization
CREB	Cyclic AMP response element binding protein
CRF	Corticotropin-releasing factor
DAG	Diacylglycerol
DAT	Dopamine transporter
DHNK	Dihydronorketamine
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
ECG	Electrocardiogram
ECS	Electroconvulsive shock
ECT	Electroconvulsive therapy
eEF2	Eukaryotic elongation factor-2
EEG	Electroencephalogram
ERK	Extracellular signal-regulated kinase; MAPK
FDA	Food and Drug Administration
FRS2	Fibroblast growth factor receptor substrate 2
FST	Forced swim test
GABA	Gamma-aminobutyric acid
GHB	Gamma hydroxybutyric acid
GSK3	Glycogen synthase kinase 3
HC	Hippocampus
HCN	Hyperpolarization-activated cyclic nucleotide-gated

HDRS	Hamilton Depression Rating Scale
HNK	Hydroxynorketamine
HPA	Hypothalamus-pituitary-adrenal
ICV	Intracerebroventricular
IEG	Immediate-early gene
IL	Infralimbic
IP	Intraperitoneal
IP_3	Inositol trisphosphate
IV	Intravenous
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LSD	Lysergic acid diethylamide
LTP	Long-term potentiation
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MAP2	microtubule-associated protein 2
MAPK	Mitogen-activated protein kinase; ERK
MDD	Major depressive disorder
MEK	Mitogen-activated protein kinase kinase; MAPKK
mEPSC	Miniatory excitatory post-synaptic current
mGluR	Metabotropic glutamate receptor
MOR	Mu opioid receptor
mPFC	Medial prefrontal cortex
mRNA	Messenger RNA
mTOR	Mammalian target of rapamycin
N_2O	Nitrous oxide
NaSSA	Noradrenergic and spesific serotonergic antidepressant
NDRI	Noradrenaline and dopamine reuptake inhibitor
NET	Noradrenaline transporter
NGF	Nerve growth factor
NK	Norketamine
NMDA	*N*-methyl-D-aspartate
NR2B	NMDA receptor subtype 2B
NREM	Non-rapid eye movement
PCP	Phencyclidine
PFC	Prefrontal cortex
PI3K	Phosphatidylinositol 3-kinases
PIP2	Phosphatidylinositol 4,5-bisphosphate
PKC	Protein kinase C

PLCγ	Phospholipase Cγ
PSD95	Postsynaptic density protein 95
RNA	Ribonucleic acid
rTMS	Repetitive high frequency transcranial magnetic stimulation
RUL	Right unilateral
SAL	Salience network, also saline
SC	Subcutaneous
Ser	Serine, S
SERT	Serotonin transporter
sgACC	Subgenual anterior cingulate cortex
SHY	Synaptic homeostasis hypothesis
SNRI	Serotonin and noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SWA	Slow-wave activity
tDCS	Transcranial direct current stimulation
Thr	Threonine, T
Trk	Tropomyosin related kinase
Tyr	Tyrosine, Y
UPB	Ultra-brief pulse
VGSC	Voltage gated sodium channel
VLPO	Ventrolateral preoptic nucleus
VMAT	Vesicular monoamine transporter
YMRS	Young Mania Rating Scale

Abstract

Major depressive disorder is a common and devastating psychiatric disorder. While pharmacotherapy and psychotherapy can be effective, a significant proportion of patients remain treatment resistant. Traditional antidepressants need to be taken for several weeks or months before the therapeutic effects become evident. For treatment-resistant patients, electroconvulsive therapy (ECT) is still the most effective treatment. Postictal slowing of electroencephalogram (EEG) activity has been associated with the therapeutic effects of ECT, but the mechanistic basis of this remains poorly studied. For decades this has encouraged researchers to investigate the antidepressant effects of isoflurane anesthesia with promising, but inconsistent, results. More recently, evidence of the rapid-acting antidepressant effects of subanesthetic doses of ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist and a dissociative anesthetic, has sparked a renewed interest in the development of novel antidepressant therapies. Another treatment to show positive results is nitrous oxide (N_2O), a gaseous anesthetic with NMDAR antagonist properties. One of the proposed mechanisms of ketamine's action is related to its ability to increase glutamatergic signaling, leading to further changes in synaptic potentiation and in the function of neuronal networks. These changes have been suggested to involve the actions of brain-derived neurotrophic factor (BDNF) signaling via its receptor TrkB. Downstream of TrkB, the inhibition of glycogen synthase kinase 3β (GSK3β), the induction of mammalian target of rapamycin (mTOR) mediated protein synthesis, and the consolidation of synaptic changes have been implicated in ketamine´s actions.

The first aim of this study is to investigate the molecular changes induced by isoflurane anesthesia in the adult mouse hippocampus using phosphoproteomics in the absence of *a priori* information. We find that brief isoflurane anesthesia induces 318 phosphorylation changes in a total of 237 proteins. While confirming the phosphorylation alterations on selected proteins, we also discover that various anesthetics, including urethane and ketamine, regulate these targets in a similar manner. In the second part, we investigate the effects of N_2O on molecular signatures implicated in ketamine's action. Findings reveal that N_2O produces cortical excitation, followed by the rebound emergence of slow EEG activity following gas cessation, which coincide with the phosphorylation of TrkB, GSK3β and p70S6k (a kinase downstream of mTor). Moreover, we demonstrate that these pathways become regulated during the postictal period after flurothyl-induced seizures or during slow EEG activity induced by hypnotic agent medetomidine. Notably, medetomidine is not effective in the learned helplessness test. Finally, we investigate the dose-dependent changes induced by ketamine in TrkB signaling. An acute administration of sedative-anesthetic doses of ketamine, accompanied by increases in slow EEG activity, is found to increase the phosphorylation of the investigated pathways. These changes appear independent of ketamine's metabolite hydroxynorketamine, an agent shown to have antidepressant-like behavioral effects in rodents.

In conclusion, our results provide novel evidence of a specific brain state characterized by slow EEG oscillations and the activation of molecular pathways implicated in rapid-acting antidepressant actions. These findings encourage the investigation of cortical excitation and the subsequent homeostatic increase of slow EEG oscillations as a fundamental basis of rapid-acting antidepressant treatments.

Tiivistelmä

Masennus on yleinen psykiatrinen sairaus, joka aiheuttaa mittavaa inhimillistä kärsimystä ja merkittäviä yhteiskunnallisia kustannuksia. Masennusta hoidetaan farmakoterapialla, mutta moni potilaista ei saa merkittävää hyötyä lääkkeistä useiden viikkojen tai kuukausienkaan käytön jälkeen. Näille hoitoresistenteille masennuspotilaille psykiatrinen sähköhoito on yhä tehokkain hoitomuoto. Yhdeksi sähköhoidon tehoa ennustavaksi tekijäksi on esitetty kouristuksen jälkeisen aivojen hidasaaltotoiminnan lisääntymistä aivosähkökäyrässä. Ajatus kannusti tutkijoita selvittämään isofluraanilla aikaansaadun anestesian masennuslääkevaikutuksia jo vuosikymmeniä sitten, mutta tulokset jäivät epäselviksi. Tuoreemmissa tutkimuksissa on puolestaan toistettavasti havaittu *N*-metyyli-D-aspartaatti (NMDA) -reseptoreja salpaavan ketamiinin nopea masennusoireita lievittävä vaikutus. Hiljattain kliinisessä tutkimuksessa on havaittu myös NMDA-reseptoreja salpaavan typpioksiduulin (N_2O) masennusoireita nopeasti lievittävä vaikutus. Isofluraanin ja typpioksiduulin vaikutusten taustalla olevat neurobiologiset mekanismit ovat kuitenkin yhä pääosin tuntemattomia. Ketamiinin vaikutusmekanismiksi on sen sijaan esitetty glutamatergisen hermovälityksen ja aivokuoren ärtyvyyden lisääntymistä, jonka on ajateltu johtavan muutoksiin synapsien ja hermosolujen toiminnassa. Näiden vaikutusten on esitetty aiheutuvan aivoperäisen hermokasvutekijän (BDNF) kohteena toimivan TrkB-reseptorin aktivaatiosta ja sitä seuraavista muutoksista glykogeenisyntaasikinaasi 3β:n toiminnassa ja rapamysiinin mekaanisen kohteen (mTOR) ohjaamassa proteiinisynteesissä.

Ensimmäisessä tutkimuksessa keskityimme selvittämään isofluraanianestesian aiheuttamia molekulaarisia muutoksia hiiren hippokampuksessa, jonka tutkimisessa hyödynsimme fosfoproteomiikkaa. Havaitsimme 318 fosforylaatiomuutosta 237 eri proteiinissa. Vahvistaessamme havaittuja muutoksia valikoiduissa proteiineissa havaitsimme monien eri anesteettien, kuten uretaanin ja ketamiinin, aiheuttavan samankaltaisia muutoksia. Tutkimuksen toisessa osassa selvitimme N_2O:n vaikutuksia ketamiinin säätelemiin solusignalointimekanismeihin hiiren etuaivokuorella. Ilokaasualtistuksen aikana havaittiin hermoston aktiivisuuteen liitettyjen merkkiaineiden lisääntymistä. Annostelun päätyttyä aivosähkökäyrässä havaittiin voimistunutta hidasaaltotoimintaa, jonka aikana kerätyissä aivonäytteissä havaittiin TrkB-välitteisen signaloinnin lisääntyneen. TrkB-signalointi lisääntyi myös näytteissä, jotka kerättiin flurotyylin aiheuttamien kouristuksien tai hidasaaltotoimintaa suoraan lisäävän medetomidiinin annostelun jälkeen. Medetomidiini ei kuitenkaan aiheuttanut masennuslääkkeille tyypillisiä käyttäytymisen muutoksia ns. opittu avuttomuus -mallissa. Lopuksi selvitimme ketamiinin annosriippuvaisia vaikutuksia TrkB-signalointiin hiiressä. Anesteettiset ketamiiniannokset lisäsivät aivosähkökäyrän hidasaaltotoimintaa, jonka aikana kerätyissä näytteissä havaittiin TrkB-signalointipolun aktivoituneen. Ketamiinin aiheuttamat muutokset näihin solusignalointimekanismeihin eivät näyttäisi olevan riippuvaisia sen metaboliatuotteesta hydroksinorketamiinista, jolla on esitetty olevan masennuslääkevaikutuksia koe-eläimiin.

Tutkimustuloksemme viittaavat siihen, että hidasoskillaatioilla ja ketamiinin vaikutuksiin liitetyillä solusignalointimuutoksilla olisi yhteys. Lisäksi tulokset kannustavat selvittämään, ovatko aivokuoren ärtyvyys ja sitä seuraava hidasaaltotoiminnan lisääntyminen nopeavaikutteisten masennuslääkkeiden yhteinen ominaisuus.

List of original publications

This thesis is based on the following two original publications and one manuscript:

I **Kohtala S**, Suomi T, Theilmann W, Wigren H-K, Stenberg T, Elo LL, Rokka A, and Rantamäki T: Brief isoflurane anesthesia produces prominent phosphoproteomic changes in the adult mouse hippocampus. *ACS Chemical Neuroscience* 6:749-56, 2016.

II **Kohtala S***, Theilmann W*, Rosenholm M, Penna L, Karabulut G, Uusitalo S, Järventausta K, Yli-Hankala A, Yalcin I, Matsui N, Wigren HK, and Rantamäki T: Cortical Excitability and Activation of TrkB Signaling During Rebound Slow Oscillations Are Critical for Rapid Antidepressant Responses. *Molecular Neurobiology*, doi: 10.1007/s12035-018-1364-6, 2018.

III **Kohtala S**, Theilmann W, Rosenholm M, Kiuru P, Yli-Kauhaluoma J, and Rantamäki T: Ketamine-induced regulation of TrkB-GSK3β signaling is accompanied by slow EEG oscillations and sedation but is independent of *cis*-hydroxynorketamine metabolite (submitted)

* Equal contribution

The publications are referred to in the text by their corresponding roman numerals.

1 INTRODUCTION

Depression is a disabling condition suffered by almost 350 million people worldwide (Smith, 2014). It produces immense individual suffering and is responsible for a large part of the total burden of nervous system disorders. Monoaminergic antidepressant drugs and psychotherapy constitute the main line of therapy against depression. The beneficial effects of traditional antidepressant effects typically become evident after weeks or months of continuous medication, but a significant number of patients do not respond to these treatments at all (Fava, 2003; Trivedi et al., 2008). For these treatment-resistant patients, interventions like electroconvulsive therapy (ECT) are often effective (Fink, 2001). However the use of ECT is limited by available resources, cognitive side-effects (Nuninga et al., 2018), and disrepute among the general public (Sienaert, 2016).

The discovery of the rapid-acting antidepressant effects of ketamine (Berman et al., 2000), an *N*-methyl-D-aspartate receptor (NMDAR) antagonist and a dissociative anesthetic, has brought renewed interest in the development of novel antidepressant drugs with a rapid onset of action. Ketamine produces a rapid and robust amelioration of depressive symptoms in many patients, with the effects often beginning within hours of a single intravenous infusion (Walter et al., 2014). The antidepressant effects of ketamine, however, only last from a couple of days to a few weeks. Moreover, ketamine is a drug of abuse (Dillon et al., 2003), which has undeniably limited its widespread clinical use.

Intriguingly, other anesthetic drugs have also displayed rapid-acting antidepressant properties in some clinical trials (Langer et al., 1995; Mickey et al., 2018; Nagele et al., 2015). These trials have reported similar treatment effects to ECT without some of the cognitive side effects. While several different molecular mechanisms and cellular signaling pathways have been implicated in the rapid-acting antidepressant effects of ketamine, the neurobiological basis of these effects remains obscure. Thus, further understanding of the molecular mechanisms behind the rapid antidepressant action of ECT and ketamine, as well as other anesthetics, will provide tools for both refining current practices and for the discovery of novel somatic and pharmacological treatments.

The literature review in this thesis briefly describes the history of antidepressants and associated theories of depression to provide a foundation for discussing the latest scientific knowledge regarding rapid-acting antidepressants. The experimental findings provide novel insights into the neuropharmacological mechanisms of anesthetic drugs and their putative associations with rapid-acting antidepressant effects.

2 REVIEW OF THE LITERATURE

2.1 Major depressive disorder

Major depressive disorder (MDD) is the most common mood disorder in the world (Smith, 2014), causing immense individual suffering and impairment of social and occupational functioning (Whiteford et al., 2013). It is a significant risk factor for suicide (Chesney et al., 2014) and one of the biggest contributors to the economic burden caused by diseases (Olesen et al., 2012). The estimated lifetime prevalence of MDD is close to 15% (Bromet et al., 2011), and the World Health Organization has predicted that MDD will become the most burdensome disease in the world within this century (Moussavi et al., 2007).

Major depressive disorder is a complex pathology with many levels of different symptoms and multiple possible contributing etiological factors, such as stress (Kendler et al., 1999), inflammation (Vogelzangs et al., 2012), cognitive and emotional factors (Joormann & Siemer, 2011), genetic predisposition (Dunn et al., 2015), and developmental processes (Whittle et al., 2014). Moreover, environmental factors such as maltreatment during childhood have been strongly associated with a substantially increased risk of depression in adulthood (Li et al., 2016). Depression shares features with normal emotional responses of sadness and grief, but in MDD these feelings become disproportionate to their cause and are not relieved despite the alleviation of external causes (Belmaker & Agam, 2008). Major depressive disorder is characterized by at least one depressive episode lasting for a duration of at least two weeks (Otte et al., 2016). During a depressive episode, distinctive changes in mood and loss of interest and/or pleasure in daily activities take place along with alterations in cognitive functioning, which may manifest as a diminished ability to think or concentrate. The heterogeneity of the disorder is further demonstrated by varying and sometimes opposing symptoms, such as weight loss or weight gain and insomnia or hypersomnia (van Loo et al., 2012). Importantly, sleep disturbances are very commonly associated with depressive disorders (Riemann et al., 2001).

Major depressive disorder is most prevalent in adults aged 18 to 64 years, with a median age of onset in the 20s (Kessler et al., 2003, 2012). Depressive episodes, however, may appear at almost any age. Childhood depression is rarely diagnosed partly due to a lack of research and proper criteria. Typically, the first diagnosis is made during adolescence or early adulthood (Egger & Angold, 2006). When compared to adolescents (13-17 years) or older adults (65+ years), adults (18-64 years) are twice as likely to be diagnosed with MDD

(Kessler et al., 2003, 2012). In addition, women are much more likely to be diagnosed with MDD than men regardless of the age group in question.

While major advances in understanding the complex neurobiological mechanisms behind MDD have been made, no complete mechanisms have been established that would explain all aspects of the disease. This is exemplified by the fact that the clinical diagnosis of depression and the treatments in use are still lacking objective biomarkers (Jentsch et al., 2015). Among the functional and structural alterations that have been associated with MDD are reductions in hippocampal volumes (Kempton, 2011), changes in the activity or connectivity of neuronal networks (Menon, 2011), alterations in inflammatory activity (Nusslock & Miller, 2016), and the dysregulation of brain metabolism and sleep (Breslau et al., 1996; Germain et al., 2004).

Several pharmacological and non-pharmacological treatment options exist for MDD. The most widely used pharmacotherapy is per os medication with selective serotonin/noradrenalin reuptake inhibitors (e.g. SSRIs and SNRIs), but only 35-50% of patients receive benefits from these drugs (Murrough & Charney, 2012; Trivedi et al., 2006, 2008). A significant portion of patients do not exhibit a favorable response to treatment with one or more antidepressants, and are categorized as having treatment-resistant depression (Fava, 2003). For the patients that do respond to antidepressant treatment, a significant delay exists between the initiation of pharmacotherapy and full remission. Moreover, chronically depressed patients may only begin to respond after 8 to 10 weeks of drug treatment (Keller et al., 1998). Notably, the improvement achieved with traditional antidepressants has been suggested to be minimal in milder forms of depression (Fournier et al., 2010).

Besides traditional pharmacotherapy, psychotherapy is also commonly used in treating MDD. Psychotherapy is generally estimated to be equally as effective as pharmacotherapy in treating MDD (Amick et al., 2015), and non-pharmacological therapies may be particularly helpful in preventing recurring depression (Clarke et al., 2015). Any direct comparison between non-pharmacological and pharmacological treatments is difficult due to methodological differences. Psychotherapy is rarely used alone in treating severe depression, but it may be combined with pharmacotherapy (Depression. Current Care Guidelines, 2016). On the other hand, psychological interventions may hold particular promise in treating subclinical depression and preventing the onset of major depressive disorder (van Zoonen et al., 2014).

Different neurobiological hypotheses of depression have been proposed over the years, including impaired monoamine neurotransmission, altered activity of the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation (Nusslock & Miller, 2016), impaired neurotrophic signaling and plasticity

(Duman et al., 1997), and impaired neuronal network wiring (Castrén, 2013). However, these hypotheses are not mutually exclusive, and each may contribute to different aspects of the disease. As will be elaborated upon in the following chapters, many of these hypotheses have been generated along with the accumulation of understanding of the mechanisms of action of traditional antidepressant drugs or through serendipitous clinical observations.

2.1.1 A brief history of antidepressants

Since ancient times, psychiatric ailments have been treated with natural remedies. Some of these phytotherapeutics, like *Hypericum perforatum* (St. John's Wort) (Istikoglou et al., 2010), are still in use and have been shown to produce some antidepressant effects in modern clinical trials (Linde et al., 2005). The plant *Papaver somniferum*, a source of opium and morphine, has a history of medical use that likely dates back to ancient times, as witnessed by archeological findings of Minoan artefacts (Askitopoulou et al., 2002). More documented uses of opium for melancholia are from the 18th century (Weber & Emrich, 1988). Among one of the earlier somatic treatments for depression is sleep deprivation, which essentially consists of depriving depressed patients of sleep. The first written accounts of sleep deprivation as a putative treatment for melancholia date back to the first half of the 19th century and were the work of psychiatrist JOHANN CHRISTIAN AUGUST HEINROTH (Steinberg & Hegerl, 2014). Clinical experiments of using sleep deprivation were carried out in later decades (Schilgen & Tölle, 1980). Sleep deprivation therapy is still in use in some countries.

The accounts of experimental seizure-provoking treatments for psychiatric disorders date back to the 1930s (Kalinowsky, 1986). Like all previous therapies, these methods were discovered not by understanding the etiology of the disease, but by the clinical observation of psychiatric patients. Insulin coma therapy, championed by MANFRED SAKEL, was practiced from 1933 until the late 1950s (Crammer, 2000; Jones, 2000; Shorter, 2009). In this form of therapy, psychiatric patients were put into a hypoglycemic coma using high doses of insulin. After waking up from the coma, patients were often agitated and sometimes experienced generalized convulsions (Kral & Laponte, 1956). During the 1930s, another new therapeutical concept was developed based on the idea of seizures having therapeutic effects. This new treatment was coined convulsive therapy and it was introduced mainly by the Hungarian psychiatrist LADISLAS VON MEDUNA, who experimentally induced seizures using camphor and pentylenetetrazol in psychiatric patients (Fink, 2001). Meduna's idea of the therapeutic effects of convulsive therapy was based on the observations that spontaneous seizures, such as those occurring after barbiturate withdrawal,

often resulted in the temporary loss of psychotic symptoms in schizophrenic patients (Kalinowsky, 1986). The results from using electricity to produce similar convulsions in animals were first reported in an English journal by LUCIO BINI (1938), the student of UGO CERLETTI, and the first patient trials soon followed (Aruta, 2011; Cerletti & Bini, 2018). The positive observations from early trials led to the development of ECT as an easier, less expensive, and safer alternative to chemical seizure therapies. In general, convulsive therapies were first used to treat schizophrenic patients, but they were later found out to be very effective for depression as well (Kalinowsky, 1986). After the establishment of ECT, chemical seizure therapies continued to be experimented with in the 1950s. Among novel agents used for inducing seizures was the volatile convulsant flurothyl (Esquibel et al., 1957), which demonstrated effects similar to ECT (Fink, 2014). Insulin coma therapy, however, was withdrawn in the late 1950s and has been discredited by some as a passing medical fad without proper scientific basis (Jones, 2000).

At the end of the 19th century PAUL ERLICH, who synthesized the arsenic medicine arsphenamine for syphilis, first articulated the idea that chemical substances might have specific actions on disease processes (Winau et al., 2004). He described these new pharmacotherapies as "magic bullets" that could act specifically on infections without affecting rest of the body. Following these lines, the views on how psychiatric drugs worked also changed in the 1950s (Moncrieff, 2008). In the previously dominant drug-centered perspective, psychiatric drugs were inducers of abnormal states such as sedation or stimulation, and these states were considered useful in some manifestations of psychiatric conditions. These views gave way to the new disease-centered view, in which drugs were seen to treat the underlying causes of the disease, and thus classes of drugs like antipsychotics and antidepressants were coined.

The development of the first so-called antidepressant drugs began in the 1950s, when the available pharmaceuticals for treating psychiatric disorders were few (Moncrieff, 2008). Medications against depression were mostly limited to amphetamine, which had been marketed for the treatment of mild depression since 1935 (Guttmann & Sargant, 1937), and opiates, which were used historically for many psychiatric conditions (Weber & Emrich, 1988). A completely new perspective on antidepressant development was fueled by the serendipitous discovery of the antidepressant effects of the anti-tuberculosis agent isoniazid (Pletscher, 1991). A drug with a very similar chemical structure, iproniazid, became the first pharmaceutical to be marketed solely for treating depression. It was thought to do so by inhibiting the action of the enzyme monoamine oxidase (MAO), responsible for the degradation of monoamines. This discovery was soon followed by a wave of novel monoamine oxidase in-

hibitors and tricyclic antidepressants, the first of the tricyclic drugs being imipramine. Along with the new antidepressants, the discovery of the antipsychotic drug chlorpromazine has been credited with having led the way to a new era in the treatment of mental disorders. Furthermore, these new drugs played an important role in replacing rudimentary neurosurgical procedures and also led to a decline in the use of convulsive therapies (Kalinowsky, 1986).

The introduction of the first line of psychiatric medications, the advancing understanding of the function of synapses, and the discovery of the spectrophotofluorimeter triggered the development of neuropharmacology in the mid-1950s (Ban, 2001). During the following decades, dozens of new antidepressants were developed following the basic pharmacological principle called the monoamine theory of depression (Hirschfeld, 2000). The scientific advances in receptor binding assays allowed further sophistication in drug development (Ban, 2001). The advent of modern antidepressant drugs became most evident with the work that led to the discovery of fluoxetine in the 1970s (Perez-Caballero et al., 2014). As a selective serotonin reuptake inhibitor (SSRI), fluoxetine had a much tolerable pharmacodynamic profile than the previous generation of antidepressants and proved to be a massive commercial success. The efficacy of fluoxetine suggested that selective regulation of serotonergic neurotransmission had antidepressant effects, and soon after, several new drugs appeared on the market with a similar mechanism of action. In the 1980s, the identification and separation of receptor subtypes along with genetic technology paved the way for more tailor-made antipsychotics and antidepressants (Ban, 2001). Today, molecules with slightly different receptor profiles and milder side effects are continuously being developed, but the efficacy of antidepressant drugs has not improved since the discovery of tricyclic antidepressants (**FIGURE 1**) (Cipriani et al., 2018; Undurraga & Baldessarini, 2017).

While the monoaminergic hypothesis of depression dominated the field for decades, some other lines of investigation were also carried out. In the 1960s, some clinical reports described the anxiolytic and antidepressant effects of gamma hydroxybutyrate, now known to act on both $GABA_B$ (gamma-aminobutyric acid B) and GHB (gamma hydroxybutyric acid) receptors (Bosch et al., 2012). Early work with ketamine and psychedelic drugs hinted of their potential in psychiatric use, but the research was more qualitative than quantitative in nature (Clark, 1975; Clark, 1977; Khorramzadeh & Lotfy, 1973; Wolfson & Wolfson, 2014), and was often performed in incoherent ways. In the 1980s and 1990s, pilot clinical experiments sought to examine the idea that the postictal silencing and burst-suppressing electroencephalogram (EEG) activity, also seen after ECT seizures, might produce antidepressant effects instead the seizure itself. These EEG changes seen after ECT, essentially short periods

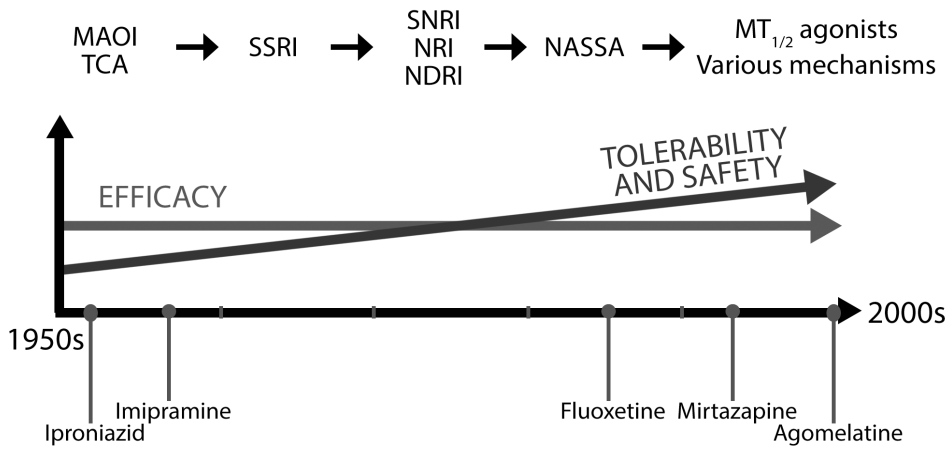

FIGURE 1. Overview of antidepressant developments. MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; SSRI, serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NRI, noradrenaline reuptake inhibitor; NDRI, noradrenaline and dopamine reuptake inhibitor; NASSA, noradrenergic and specific serotonergic antidepressant; MT, melatonin receptor.

of high-amplitude low-frequency bursts of activity, can be achieved with deep isoflurane anesthesia. This pharmacologically induced EEG burst-suppression produced by isoflurane was found to elicit antidepressant responses in patients suffering from major depression (Langer et al., 1985; Carl et al., 1988; Engelhardt et al., 1993; Langer et al., 1995). While the results from these trials were promising, showing treatment effects comparable to ECT with fewer cognitive side-effects, some groups reported limited or no beneficial effects from volatile anesthetics (Greenberg et al., 1987; García-Toro et al., 2001). Due to conflicting results and the lack of animal research, these studies did not gain much attention until recently, when Weeks et al. (2013) replicated some of Langer's initial work by demonstrating the antidepressant effects of isoflurane in a small open-label trial.

The rapid advances in understanding the nervous system along with new developments in the basic tools of molecular biology opened new perspectives in examining antidepressant effects in preclinical research. The discovery of nerve growth factor (NGF) in the early 1950s by RITA LEVI-MONTALCINI and VIKTOR HAMBURGER (Levi-Montalcini & Hamburger, 1951) was followed decades later by the discovery of brain-derived neurotrophic factor (BDNF) (Barde et al., 1982). These neurotrophins were found to have essential roles in mediating the development of the nervous system (Davies, 1994; Huang & Reichardt, 2001), but also in mediating neuronal plasticity in the adult

brain (Poo, 2001; Thoenen, 1995). Moreover, the discovery of neurotrophins paved the way for the seminal work done by RONALD DUMAN and colleagues, who demonstrated that monoaminergic antidepressants and electroconvulsive shock (ECS; a rodent model of ECT) produced gradual increases in the synthesis of BDNF in the hippocampus and cortex of rodents (Nibuya et al., 1995). Taken together, these discoveries led to the presentation of a molecular and cellular theory of depression, with the regulation of neurotrophic factors and neuronal plasticity by antidepressants being one of the key mechanisms of action (Duman et al., 1997). Since then, some scientists have suggested that traditional antidepressants act as "plasticity enhancers" capable of reactivating sensitive period-like plasticity and brought up questions about the importance of psychotherapy in conjunction with antidepressants (Castrén, 2013; Castrén & Hen, 2013).

The work of PHIL SKOLNICK and colleagues linked antidepressant-like behavioral outcomes in animal models to NMDARs (Trullas & Skolnick, 1990). In another study, a link between the chronic administration of traditional antidepressants and alterations in NMDAR subunit messenger RNA (mRNA) expression was discovered (Boyer et al., 1998). Following these findings, a major breakthrough in depression research came with a clinical study that demonstrated the rapid-acting antidepressant effects of subanesthetic ketamine (Berman et al., 2000). Ketamine was not only found to provide rapid amelioration of depressive symptoms, but to have efficacy in treatment-resistant and suicidal MDD patients. These findings marked a shift in approaching the pharmacological basis of antidepressant effects from monoaminergic neurotransmission to glutamatergic neurotransmission. Importantly, the fact that ketamine, also a drug of abuse, could be administered in small dosages that elicited only minor psychoactive effects was promising for the development of non-psychoactive novel molecules. In the following decades, a myriad of drug candidates targeting glutamatergic neurotransmission emerged, but they have had relatively little clinical success so far. The preclinical studies of ketamine have, however, strengthened the association of neurotrophic signaling, synaptogenesis, and neurogenesis with the mediation of antidepressant effects (Duman & Aghajanian, 2012; Ma et al., 2017).

Evidence of other putative rapid-acting antidepressants besides ketamine have emerged in the recent years. One small pilot study recently demonstrated the promising rapid-acting effects of the anesthetic gas nitrous oxide (N_2O) in the treatment of MDD (Nagele et al., 2015). Even more recently, psychedelic drugs like psilocybin, targeting the 5-hydroxytryptamine receptor 2A (5-HT_{2A}), have regained attention regarding their role in the treatment of psychiatric disorders. The most recent evidence regarding psilocybin comes from a pilot

clinical trial where the drug was found to produce rapid and long-lasting antidepressant effects in a small sample of MDD patients (Carhart-Harris et al., 2016). Along with these findings and the re-introduction of psychedelic drugs to modern neuroscience, old perspectives on the importance of the psychological experience in a therapeutic context have been brought back into modern discussion (Carhart-Harris et al., 2018).

2.1.2 Major hypotheses of depression and antidepressant action

The monoamine hypothesis of depression has unarguably had the largest impact on the research of antidepressant drugs and depression to date. This hypothesis was formulated following several different converging observations regarding the role of monoamines and especially serotonin in brain function and drug action. Intriguingly, one of the key drivers for this progress was the surge in scientific research conducted with the then recently discovered lysergic acid diethylamide (LSD), which was found to block the effects of serotonin on peripheral receptors and to cause strong hallucinogenic effects in humans (Woolley & Shaw, 1954). However, before the role of serotonin in the brain was discovered, the pharmacological properties of serotonin were mostly associated with its ability to cause smooth muscle contractions and subsequent vasoconstriction – hence the term serotonin, or "serum tonic". VITTORIO ERSPAMER extracted a compound from enterochromaffin cells and named it enteramine in 1937 (Ersparmer & Viallu, 1937). Later, it was found to be the same compound as serotonin (Erspamer & Asero, 1952), which was separately discovered by MAURICE RAPPORT and colleagues (Rapport et al., 1948) and characterized as 5-hydroxytryptamine (5-HT) (Rapport, 1949). Just a few years after the discovery of serotonin, Woolley and Shaw (1954) first speculated that the mental aberrations produced by LSD were the result of the substance interfering with the function of serotonin in the brain. While vivid debates on the role of serotonin in the central nervous system were launched ("The Role of Serotonin in the Central Nervous System," 1956), the notion of chemical transmission in the brain prevailed, and monoaminergic neurotransmitters began to be considered crucial for controlling brain activity (Gaddum, 1963).

Findings related to the drug reserpine, an antihypertensive drug extracted from the plant *Rauwolfia serpentina*, formed another important link between noradrenaline, serotonin, and depression (Pletscher, 1991). Reserpine was found to inhibit vesicular monoamine transporters (VMAT) responsible for the transport of intracellular monoamine transmitters into presynaptic vesicles and to deplete the brain of monoamines in large doses (Brodie et al., 1955), precipitating depressive symptoms in some individuals (Muller et al., 1955). Both serotonin and reserpine were found to act as sedatives in mice and could

potentiate the action of other hypnotic drugs. These effects could be counteracted by pretreating the animals with LSD (Shore et al., 1955). Noradrenaline could not be ruled out as a mediator either, since the precursor to noradrenaline, dihydroxyphenylalanine, has been effective in reversing reserpine induced effects in animals (Carlsson et al., 1957).

Another line of evidence came along with the discovery of the euphoric and stimulating effects of the tuberculosis drugs isoniazid and iproniazid (Crane, 1956). Iproniazid was discovered to act as an inhibitor of monoamine oxidases (MAOI), which are enzymes responsible for the oxidative deamination, or inactivation, of free intracellular monoamine neurotransmitters. Essentially, pre-administration of iproniazid was found to reverse the action of reserpine by sparing cytosolic monoamines from inactivation and turning reserpine's sedative effects into stimulation (Pletscher, 1991). These findings were well in line with the notion that increasing the synaptic concentrations of monoamines led to the relief of depressive symptoms, and these observations were one of the key factors in the development of the monoamine hypothesis (Bunney & Davis, 1965; Hirschfeld, 2000; Schildkraut, 1965). In particular, the monoamine hypothesis proposed that depression is a disease manifested by reduced levels of noradrenaline, dopamine, and/or serotonin in the brain, and that this could be counteracted by the inhibition of the enzyme responsible for breaking down these substances.

The discovery of the antidepressant effects of imipramine, the first of many antidepressant drugs with a tricyclic structure, did not at first fit into the initial monoamine theory since it only marginally affected MAO enzymes (Pletscher, 1991). Imipramine was originally developed as a sedative anxiolytic for use in agitated psychotic patients. Its use as an anxiolytic was unsuccessful because it had the tendency to provoke manic effects, but patients with depression showed remarkable stimulation and relief (Kuhn, 1958). After the serendipitous discovery of its antidepressant potential, imipramine was found to inhibit the reuptake of noradrenaline and serotonin, with lower doses acting as stimulant and higher doses producing sedation in animals (Maxwell & Palmer, 1961). A number of drugs were produced based on the tricyclic structure following imipramine, and these had potent effects on both serotonin and noradrenaline (Hillhouse & Porter, 2015; Owens et al., 1997). Tricyclic antidepressants, however, possess a number of off-target effects to muscarinic, adrenergic, and histaminergic receptors that lead to a wide variety of unwanted side effects, such as sedation, dry mouth, blurred vision, and hypotension (Gillman, 2007). In the 1960s, evidence from a postmortem study indicated that the levels of serotonin in the hindbrain were decreased in depressed patients that had conducted suicide (Shaw et al., 1968), and other studies indicated the

mood-promoting effects of the serotonin precursor tryptophan in conjunction with MAOIs (Coppen et al., 1963; Pollin et al., 1961). These and other studies further advanced understanding of the role of serotonin in mediating mood.

To combat both the side effects of tricyclic antidepressants and the primary target of rational drug design, the development of more pharmacologically specific drugs began. Indeed, drugs such as fluoxetine, sertraline, and citalopram addressed some issues of safety and tolerability by being more selective to serotonin reuptake inhibition without potent off-target effects (Owens et al., 1997). Following the success of SSRIs, drugs that selectively target noradrenaline reuptake inhibition (NRIs), like reboxetine, or drugs that target serotonin and noradrenaline reuptake (SNRIs), like duloxetine, were also been developed. In addition, a group of drugs labeled as atypical antidepressants have primary targets other than the regulation of serotonin and/or noradrenaline. This class consists of a wide variety of drugs with targets varying from noradrenaline and dopamine reuptake inhibition (NDRIs, e.g. bupropion) to noradrenergic and specific serotonergic antidepressants (NaSSAs, e.g. mirtazapine) and melatonin receptor agonists (e.g. agomelatine). Despite the triumph of more selective antidepressants, some tricyclic antidepressants are still in active clinical use and their antidepressant effects are comparable to SSRIs (Cipriani et al., 2018; Undurraga & Baldessarini, 2017).

The monoamine hypothesis continued to gather strong support until the last few decades, when contradicting hypotheses and evidence surfaced. For example, more recent evidence indicates that monoamine depletion in healthy subjects does not provoke episodes of depression (Salomon et al., 1997), and that the depletion of monoamines or tryptophan levels does not increase depressive symptoms in MDD patients without medication (Berman et al., 2002). In a meta-analysis of monoamine depletion studies, decreased mood was demonstrated only in patients with a family history of MDD and in patients who are not currently on medication and have MDD in remission (Ruhé et al., 2007). This meta-analysis also concluded that these depletion studies fail to demonstrate a causal relationship between monoamine depletion and MDD. It is, however, possible, that different paradigms of depletion and prolonged depletion periods could have more pronounced effects in provoking depression.

Another line of evidence against the monoamine hypothesis of depression comes from the acute pharmacological action of antidepressant drugs. Since most of these drugs elicit their effects on synaptic concentrations of monoamines within hours of drug administration, antidepressant effects could be expected to be almost immediate. However, the antidepressant effects become evident only after weeks or months of continuous treatment. For example, in a trial by Glassman and Platman (1969), treatment with MAOI

and tryptophan had an onset of 7 to 21 days, though the treatment is expected to produce an immediate increase of serotonin in most brain areas. This delay in antidepressant effects is a critical concern in clinical practice, where patient compliance is important and suicidal symptoms are sometimes present. Moreover, it is well known that the adverse effects of antidepressants often manifest rapidly after treatment initiation, which further indicates immediate effects on monoamines. Another clinically relevant problem is that many patients do not respond to any traditional antidepressant treatments, but remain pharmaco-resistant. Were depression a disease only dictated by insufficient monoamine activity in the sense of the traditional hypothesis, relief would be achieved by increasing monoamines with the many means available to clinicians today.

The growing body of evidence against the monoamine hypothesis has encouraged researchers to look for new neurobiological clues that could explain antidepressant effects beyond monoamines. Refinements to the original hypothesis have also been made, such as the addition of new mechanistic layers including the regulation of monoamine receptor dynamics (Charney et al., 1981; Zemlan & Garver, 1990). A hypothesis born out of these new ideas proposed that the regulation of neurotransmitter release by serotonin autoreceptors is crucial in explaining the delayed onset of action of antidepressant drugs (Blier & de Montigny, 1994; Stahl, 1998). These receptors are located not only on the postsynaptic terminal, but also in the cell body, as in the case of 5-HT_{1A} receptors (Hannon & Hoyer, 2008; Sprouse & Aghajanian, 1987; Weissmann-Nanopoulos et al., 1985), or in the vicinity of presynaptic axon terminals, as in the case of 5-HT_{1D} receptors (Hannon & Hoyer, 2008; Hoyer & Middlemiss, 1989; Waeber et al., 1990), where they have regulatory roles in controlling neuronal activity and transmitter release. The stimulation of 5-HT_{1A} autoreceptors located in the raphe nucleus, where most serotonergic neuronal cell bodies reside, decreases the firing of these neurons and thus reduces the amount of 5-HT released from neuronal projections (Rutter et al., 1995; Sprouse & Aghajanian, 1987), a phenomenon known to happen during physiological activity and acutely after SSRI treatment (Bel & Artigas, 1992; Chaput et al., 1986; Invernizzi et al., 1992). Chronic treatment with SSRIs, however, results in the desensitization of 5-HT_{1A} receptors, which leads to the disinhibition of neuronal activity and increased serotonergic neurotransmission. Indeed, increased levels of extracellular 5-HT have been observed in some chronic studies (Bel & Artigas, 1993; Rutter et al., 1994), but not in all (Hjorth & Auerbach, 1994). Following this idea, it has been suggested that the continuous presence of SSRIs might be important to maintain high enough extracellular 5-HT levels for the therapeutic effects (Invernizzi et al., 1996).

Intriguingly, many antidepressant drugs with atypical pharmacological profiles that do not easily fit the confines of even the refined monoamine hypothesis have also been discovered. Some of these drugs, such as tianeptine and mianserin, date back to the 1960s, while others have been developed more recently, like mirtazapine and agomelatine. For example, tianeptine does not inhibit serotonergic, dopaminergic, or noradrenergic transporters or receptors, but may in fact increase serotonin uptake (Kasper & McEwen, 2008; Mennini et al., 1987). Interestingly, tianeptine's main action has been proposed to be mediated through μ-opioid receptors (MOR) (Gassaway et al., 2014; Samuels et al., 2017). Moreover, many antidepressants are prescribed today for a variety of conditions ranging from obsessive compulsive disorder to social phobia and post-traumatic stress disorder (Schatzberg, 2000), which has prompted discussion on the validity of calling these drugs antidepressants (Lara & Souza, 2001). Novel therapeutic approaches have been warranted, and the development of new drugs based on old principles have been discouraged by some researchers (Agid et al., 2007).

Alternative views on the importance of monoamine transmission in the mechanism of action of antidepressants have also been expressed. For example, Heninger et al. (1996) state that monoaminergic systems are more modulatory in nature and may interact with other systems to produce antidepressant effects. They proposed that antidepressant effects may manifest through the modulation of different systems, for example, by affecting glutamatergic neurotransmitters and normalizing the function of the HPA axis, by altering neurotrophin signaling, or through effects on immune systems and various intracellular cascades. Indeed, many of these areas of research have gathered increasing attention in the last decades. Some researchers have also proposed the idea of serotonin playing a completely opposite role, so that serotonin transmission is in fact increased in depression (Andrews et al., 2015).

Abnormalities in the activity of the HPA axis have been proposed to play a key role in the etiology of depression (Ehlert et al., 2001; Gold & Chrousos, 2002; Gold et al., 1988; Holsboer, 2000; Merali, 2004). Essentially, stress-causing stimuli lead to the activation of the autonomic sympathetic nervous system and the HPA axis. While the autonomic nervous system is responsible for the acute and rapid stimulation of adrenaline secretion by the adrenal glands, the HPA axis uses corticotropin releasing factor (CRF) as its first-line messenger (Chrousos & Gold, 1998). Corticotropin releasing factor is released from the paraventricular nucleus of the hypothalamus and further stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary, which results in the synthesis and release of the glucocorticoid hormone cortisol (corticosterone in rodents). Glucocorticoids serve several functions, from catabolic action to

the suppression of the immune system. Most importantly, glucocorticoids play a key role in the homeostatic regulation of stress responses. A study investigating the pituitary volume of treatment-naive pediatric patients found that MDD patients had significantly larger pituitary gland volumes than healthy controls. The biggest differences were observed in boys suffering from nonfamilial MDD (MacMaster et al., 2006)

While normal responses to stress, as regulated by the HPA axis, are typically adaptive and help an organism to cope with stress-inducing situations, excessive and prolonged stress responses can have harmful effects. For example, early life stress has been reported to cause changes in the ability of the HPA axis to respond to stress during adulthood and is associated with an increased risk of psychiatric disorders (Heim et al., 2008; Martins et al., 2011). In addition, the incidence of major depressive episodes is associated with more frequent stressful life events (Hammen, 2005). During chronic stress, glucocorticoid levels are elevated, which can produce atrophic changes in the hippocampus. This is supported by findings that depression duration predicts hippocampal volume loss in otherwise healthy women (Sheline et al., 1999). Additional evidence has been found in studies detecting decreased neurogenesis, synaptogenesis, and dendritic spines in relation to stress (Egeland et al., 2015). Moreover, patients who suffer from Cushing's syndrome, characterized by abnormally high levels of circulating cortisol, often show depressive symptoms and atrophic changes in the hippocampus (Starkman et al., 1992; Starkman & Schteingart, 1981). However, not all patients display abnormalities in the HPA axis, while some types of depression are overrepresented when HPA changes are examined (Stetler & Miller, 2011).

A systematic review looking at atypical and melancholic depressive subtypes found that melancholic depression is especially associated with increased cortisol levels (Juruena et al., 2018). Elevated cortisol in depression may be caused by issues at different levels of regulation, including impairment of the negative feedback from glucocorticoid receptors (Boero et al., 2018), increased responsiveness of the adrenal glands to circulating ACTH, and the abnormal secretion of CRF. Taken together, these findings have encouraged investigators to seek potential targets of drug development. In animal studies, centrally administered CRF has been reported to reduce exploratory behavior in novel environments and to cause stress-induced freezing behavior, among other behavioral changes (Dunn & Berridge, 1990), while CRF antagonists have been found to reverse some of these outcomes (Heinrichs et al., 1995). Antagonists targeting glucocorticoid and CRF receptors have been developed and tested for treating depression and anxiety disorders among other uses, but such drugs have not yet entered the market. While some positive results have been report-

ed with CRF_1 antagonists attenuating stress responses in primates (Habib et al., 2000) and reducing the effects of chronic mild stress in behavioral paradigms of mice when combined with fluoxetine (Ducottet et al., 2003), CRF antagonists have failed to produce antidepressant-like behavioral effects in rats tested with the forced swim test (FST) (Jutkiewicz et al., 2005).

The forced swim test is one of the most widely used behavioral models in the characterization of monoaminergic antidepressants, in which a rodent is placed in a beaker filled with water, unable to escape from the water and the confined space. The injection of an antidepressant drug prior to the testing typically results in an increased time spent actively swimming before settling for passive floating. This effect is typical to most monoaminergic antidepressants and has served as an excellent predictor of antidepressant potential in new drug candidates, since up to 90% of clinically effective antidepressants show significant results in the FST (Borsini & Meli, 1988). This test, however, may not be optimal for measuring putative antidepressants with novel mechanisms of action. Comprehensive clinical trials may be required to further assess the potential of CRF antagonists in depression.

The wide array of non-antidepressant applications of antidepressant drugs and the discovery of the regulation of neurotrophic factors by antidepressants formed the basis for the neurotrophin hypothesis of depression (**FIGURE 2**). This important hypothesis revolves around the idea of depression being the consequence of insufficient neurotrophic signaling, leading to impaired connectivity and survival of neurons especially in brain areas important for mood regulation (Duman et al., 1997). This hypothesis is supported by the preclinical findings that stress and glucocorticoid injections could decrease the expression of BDNF and promote atrophy of hippocampal neurons (Smith et al., 1995), while chronic antidepressant treatment (Dwivedi et al., 2006), ECS (Nibuya et al., 1995), or exercise (Russo-Neustadt et al., 1999) could prevent this down-regulation in rodents. Subsequently, neurotrophic factors and plasticity-related signaling pathways became a major branch of depression research.

Indeed, continuous antidepressant administration to rodents subjected to chronic stress can reduce immobility time in the FST and prevent the reduction of sucrose consumption in the sucrose preference test (Haenisch et al., 2009), which are thought to be markers of antidepressant-like action. The sucrose preference test measures the preference animals have for drinking a sweet sucrose solution compared to water. A decrease in preference is thought to be indicative for anhedonia. Furthermore, evidence linking BDNF to antidepressant-like behavioral responses in the learned helplessness (LH) model and FST in rats have been demonstrated in studies investigating direct infusions of BDNF into the midbrain (Siuciak et al., 1997) and the dentate gyrus

of the hippocampus (Shirayama et al., 2002). Similar results have also been achieved using intracerebroventricular infusion in rats, from which the effects on FST were found to persist for six days after a single infusion (Hoshaw et al., 2005). In addition, reduced BDNF expression levels have been measured post mortem in the brains of suicide victims (Dwivedi et al., 2003) and serum levels of BDNF have been found to be lower in the serum of depressed patients (Molendijk et al., 2014). Increased BDNF expression in the hippocampus of depressed patients has been noted after antidepressant treatments (Chen et al., 2001).

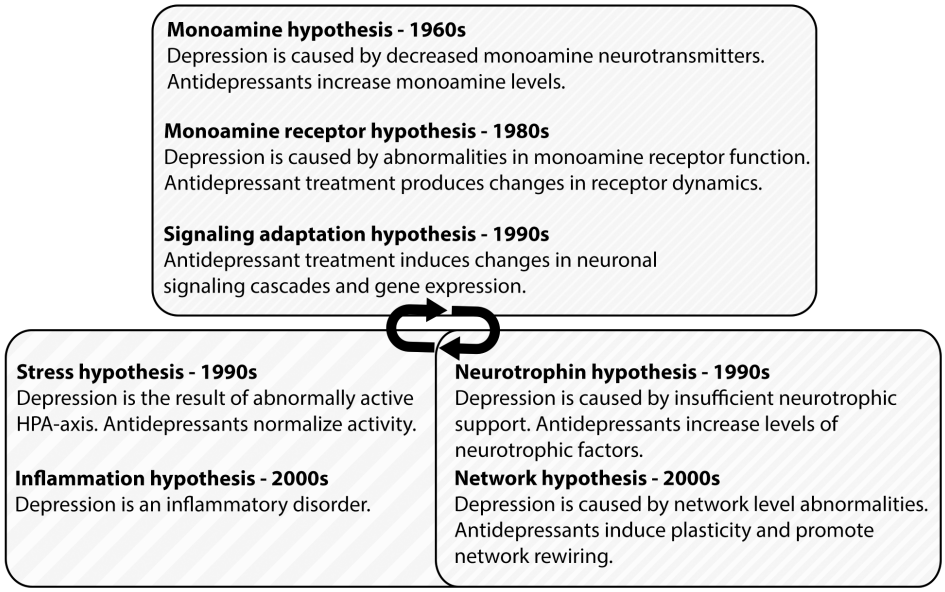

Figure 2. Overview of some of the major hypotheses of depression.

In addition to the neurotrophin hypothesis, the network hypothesis of depression has also been discussed in the scientific literature. While the neurotrophin hypothesis suggests that insufficient neurotrophic support underlies depression, the network hypothesis postulated that the amelioration of depression is the result of increased plasticity and consecutive adaptations in neuronal networks, and that this network wiring could be modified by increasing neuroplasticity through antidepressant drugs and activity-dependent processes (Castrén, 2013). Most importantly, this hypothesis accounts for the delay in the onset of action of traditional antidepressant drugs and suggests that antidepressant treatments may be most effective when combined with

psychotherapy. Since neuronal plasticity and the shaping of neuronal networks are activity-driven processes (Hensch, 2005), environmental guidance may play a key role (Castrén, 2013; Castrén & Hen, 2013). Indeed, this idea is supported by the ability of the antidepressant drug fluoxetine to reintroduce juvenile-type plasticity in the rat visual cortex and to facilitate recovery from developmental amblyopia (i.e. reduced vision in one eye due to closing of the eye during a sensitive period) (Vetencourt et al., 2008). Similar effects have been observed in mice using fear conditioning, where a combination of extinction training with fluoxetine produced a sustained loss of conditioned fear responses (Karpova et al., 2011). This suggests that similar phenomena might be occurring in mood-related circuitry.

Built upon the foundations of the neurotrophin and network hypotheses of depression, a hypothesis called undirected susceptibility to change proposes that SSRI treatments do not enhance mood as such, but amplify the influence of external conditions on the depressed patients (Branchi, 2011). Several lines of preclinical and clinical studies have recently emerged that support such an idea. For example, mice subjected to chronic stress and treated with fluoxetine in an enriched condition improved their depression-like symptoms in behavioral tests, while stressful conditions led to worsening of behavioral responses (Alboni et al., 2017; Branchi et al., 2013). Moreover, citalopram has been suggested to produce antidepressant outcomes that are dependent on socioeconomic status (Viglione et al., 2019) and living conditions (Chiarotti et al., 2017). Further research is required to elucidate the complex interactions between SSRI treatment and environmental factors, and whether they are of significant clinical importance.

2.2 Rapid-acting treatments of depression

Clinical depression is likely to develop slowly, with functional alterations taking place long before major depressive episodes appear. While traditional antidepressants take time to ameliorate depressive symptoms, rapid-acting treatments of depression can be characterized by the rapid (within days) or almost immediate (within hours) relief of depressive symptoms after a single treatment. The question of how such alterations can develop so slowly yet be remedied so rapidly remains unanswered. Despite gaps in understanding the mechanisms of action behind rapid-acting treatments of depression, two clinically effective treatments are in active use. These are electroconvulsive therapy and the intravenous administration of ketamine. Emerging evidence indicates that several other putative rapid-acting antidepressant treatments may also exist. In this chapter, clinical and preclinical research on rapid-acting antidepressant treatments that have demonstrated efficacy in clinical trials is reviewed from neuropharmacological and neurobiological perspectives.

2.2.1 Electroconvulsive therapy

The use of ECT as a psychiatric treatment began in the late 1930s (Bini, 1938; Cerletti & Bini, 2018). Electroconvulsive therapy is still in widespread use and remain one of the most effective and rapid treatments for MDD, in particular for pharmacoresistant depression. Many different treatment protocols exist, and they vary according to the disease being treated, since ECT is also widely used for the treatment of other disorders like mania (Small et al., 1985) and schizophrenia (El-Islam et al., 1970). The current form of ECT consists of a brief pulse of electrical stimulation under anesthesia, oxygenation, and continuous monitoring. This makes modern ECT much safer and more effective than the historical treatments. The effectiveness of ECT in the treatment of depression has been well demonstrated, and shown to be superior to pharmacotherapy (Giacobbe et al., 2018; Husain et al., 2004; UK ECT Review Group, 2003).

When compared to traditional pharmacotherapy, ECT produces a more rapid alleviation of depressive symptoms (Husain et al., 2004; Spaans et al., 2015). Electroconvulsive therapy is most often delivered as a series of 6 to 12 treatments, typically three times a week, and a reduction in depressive symptoms is typically seen in 2-4 weeks. It has been reported that over half of the patients treated with ECT received an initial response already within the first week of treatment (Husain et al., 2004). Electroconvulsive therapy treatment also reduces suicidality to a greater degree than traditional pharmacotherapies (Kellner et al., 2005). From a clinical perspective, this relatively rapid action is

particularly important in severely depressed and suicidal patients. Systematic monitoring of treatment responses is important, especially since premature discontinuation can lead to relapse of depression.

While ECT is an effective treatment, it can also cause clinically significant adverse cognitive effects in some patients (Nuninga et al., 2018). These vary from mild memory problems to more severe (and rare) delirium. Research has demonstrated that cognitive functions do recover in the following months after the treatment, but concerns about the safety of ECT remain persistent. Obbels et al. (2018) demonstrated that no significant long-term cognitive side effects were visible six months post-ECT in any of the neuropsychological measurements investigated in late-life depressed patients. Similar results were also obtained by Nuninga et al. (2018), who reported acute negative cognitive effects, but also recovery after six months. Partly fueled by gruesome depictions of ECT in popular culture (Sienaert, 2016) and the misunderstanding that ECT severely damages the brain and cognition, many patients refrain from considering ECT as a treatment option. While studies on humans and nonhuman primates have not demonstrated any evidence of anatomical changes (Dwork et al., 2004; Sheryl et al., 2015), further research using modern imaging methods is warranted (Oltedal et al., 2015). Due to some of the aforementioned issues, ECT is sometimes, perhaps improperly, considered a last resort after all other treatment options have failed.

The mechanisms of action behind the therapeutic effects of ECT remains a mystery. Many different hypotheses have been proposed, including monoaminergic, neuroendocrine, and neuroplasticity-centered perspectives. While most of the evidence for molecular mechanisms has been derived from animal models using ECS treatments, new evidence from modern human neuroimaging studies has also emerged in recent years.

2.2.1.1 Clinical administration of ECT

A typical course of ECT takes place in the morning after a night of fasting (K. Järventausta, personal communication, 23.11.2018). It consists of placing sets of electrodes on the scalp of the patient to monitor EEG and lead the electric current to the brain, electrodes on the chest for monitoring the electrocardiogram, a blood pressure cuff around the arm, and a pulse oximeter in the finger. Patients are not typically intubated, but oxygen is administered through a mask. A needle is placed into a vein in the arm for the intravenous administration of medication. Since many medications may interact with ECT, medications are usually discontinued before the initiation of the treatment course (Lisanby, 2007). The patient is then anesthetized, either using a volatile anesthetic or an intravenous one, and given a neuro-muscular blocking agent such as succinyl-

choline for muscle relaxation. Motor symptoms of a seizure are also monitored. This can be achieved by allowing muscle contraction in a limb, for example, for by using a tourniquet around the patient's ankle before the administration of a muscle relaxant. Atropine or other drugs may be used to reduce bradycardia and bronchial secretions. During an optimal state of anesthesia, a brief pulse of electrical current is passed through the brain. The goal is for this current to trigger a generalized cerebral tonic-clonic seizure that affects the entire brain.

The successful delivery of ECT requires the placement of two electrodes on the scalp. The location of the electrodes may differ, with many varying configurations possible (Lisanby, 2007). The location of the electrodes and the intensity of the current affects both the efficacy of the treatment and the profile of adverse effects (Sackeim et al., 2000). Bitemporal or bilateral (BT), right unilateral (RUL), and bifrontal (BF) are the electrode placements used most frequently (Lisanby, 2007). The dose of ECT is measured in millicoulombs, and an effective dose must be sufficient to induce seizure activity. A typical approach is the selection of appropriate dosage based on seizure-threshold titration, in which progressively higher amounts of charge are delivered in subsequent treatment sessions until a dose above the established seizure threshold is selected.

In the beginning, ECT was given using sine wave stimulation, but this method has been since found to be inefficient for seizure induction and have a pronounced profile of adverse cognitive effects (Prudic, 2008). Today, brief pulse waveform is more commonly used, since it produces an equivalent level of efficacy and a much better profile of postictal function (Fujita et al., 2006). In brief pulse stimulation, peak stimulus intensity is reached rapidly, reducing the amount of excess energy transmitted after neuronal depolarization. Typically used pulse widths range from 0.5 to 2 milliseconds (Prudic, 2008). Ultra-brief pulses of less than 0.5 milliseconds have also been investigated and found to produce fewer cognitive deficits, while still producing sufficient treatment efficacy (Loo et al., 2015).

After the treatment, patients may feel confused and disoriented – partly due to anesthesia and partly due to the treatment itself. This state of confusion is typically not long lasting (Lisanby, 2007). Memory loss can be present during the course of ECT treatments, but memory should gradually return to normal after the treatments have been stopped. Amnesia of events shortly before, during, and after treatment can occur. Other typical but passing side effects include headaches and nausea. The frequency of ECT administration, electrode placement, stimulus waveforms, pulse width, and intensity of electrical charge also contribute to the profile of adverse cognitive effects (Prudic, 2008; Weiner et al., 1986).

2.2.1.2 Research on the mechanisms of ECT

Once an electrical pulse is released from the ECT electrodes, it travels through intermediary tissue to the brain and forces stimulation into groups of neurons by altering their electrical surroundings and concentrations of ions (Singh & Kar, 2017). Groups of neurons then begin to fire simultaneously, which produces the propagation of seizure activity. This abnormal electrical activity generalizes throughout the brain and affects brain structures from the cortex to hypothalamus and the basal ganglia, although certain brain areas might be more specifically involved (Enev et al., 2007). Since methods like repetitive high frequency transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) also stimulate the brain and may act as antidepressants without producing seizure activity, it has been proposed that the stimulation induced by ECT may also be beneficial, albeit less so than the generalized seizure following it (Swartz, 2014).

While the therapeutic efficacy of ECT is traditionally attributed to a generalized seizure, a seizure is not sufficient for achieving the therapeutic response. Other EEG characteristics have been intensively studied in recent decades using computational methods (Mayur, 2006). For example, a low dose of RUL ECT has been demonstrated to be relatively ineffective despite producing a generalized seizure (Sackeim et al., 1987). The duration of seizure activity has also been previously considered to be a marker for adequate therapeutic response (Maletzky, 1978), but other studies indicate that this is not likely to be the case (Gangadhar et al., 1999; Krystal et al., 1993; Nobler et al., 1993; Weiner et al., 1986).

On the other hand, changes in EEG after an ECT treatment may predict the clinical outcome. The most common EEG finding thought to be associated with the clinical outcome is the slowing of EEG activity during the treatment course, especially in the frontal cortex in the delta frequency band (~1-4 Hz) (Fink & Kahn, 1957; Perera et al., 2004; Sackeim et al., 1996). It is well known from studies of epilepsy that seizures are followed by an immediate period of EEG slowing or postictal depression (So & Blume, 2010). The slowing of EEG during and acutely after the course of convulsive therapies has been well documented (Chusid & Pacella, 1952; Kriss et al., 1978; Silfverskiold et al., 1987), and appear to be similar in both ECT and pharmacological convulsant treatments (Chatrian & Petersen, 1960). It has also been observed that more pronounced postictal slowing after a single ECT session is associated with more rapid responses to ECT (Folkerts, 1996) and clinical improvement (Nobler et al., 1993; Suppes et al., 1996). Alternatively, different analysis methods such as the fractal dimension of EEG signal can be applied. In a study by Gangadhar et al. (1999), smaller postictal fractal dimension (smaller values corresponding

to a more isoelectric EEG) at a first ECT predicted remission status after six ECTs. Furthermore, increased delta activity has been also suggested to underlie clinical improvement after pharmacological and psychotherapeutic interventions (Buysse et al., 1997). Taken together, this evidence indicates that the modulation of cortical slow oscillatory activity seems to be intimately connected to the mechanisms by which ECT provides its therapeutic efficacy.

Among other markers of efficacy, the upregulation of circulating BDNF levels after ECT has been proposed as a putative marker of treatment response. Three meta-analyses have focused on the changes in peripheral blood BDNF levels after ECT treatment with patients suffering from MDD (Brunoni et al., 2014; Polyakova et al., 2015; Rocha et al., 2016). The meta-analysis by Polyakova et al. (2015) consisted of four studies, with a total of 108 patients, looking at plasma BDNF levels, and found an increase following ECT. A positive correlation between plasma BDNF levels and the number of ECT treatments was also noted. In another meta-analysis by Rocha et al. (2016), results from nine studies, with a total of 207 patients, indicated that BDNF levels in serum or plasma increased in MDD patients following ECT treatments. Finally, Brunoni et al. (2014) looked at 11 studies, with a total of 221 patients, and found that when combining serum and plasma data, BDNF levels increase after ECT. However, it is important to note that none of above meta-analyses show a relationship between BDNF changes and antidepressant responses. Contrasting results have also been published, with Ryan et al. (2018) reporting no difference in plasma BDNF levels 1-3 days after the end of ECT treatment. In their study, 61 medicated MDD patients and 50 healthy controls were investigated. They also reported no differences in levels of plasma BDNF between baseline controls and medicated MDD patients or between ECT responders and non-responders.

The regulation and function of blood BDNF is poorly understood. Human platelets are known to be rich in BDNF (Fujimura et al., 2002; Rosenfeld et al., 1995), which is released during blood coagulation and can be easily measured from serum (Naegelin et al., 2018). A recent study reported that human and rat megakaryocytes express BDNF mRNA in a similar manner to neurons, though BDNF was undetectable in mouse megakaryocytes – a finding in line with the absence of BDNF in mouse serum (Chacón-Fernández et al., 2016). These results suggest that megakaryocytes are the main source of blood BDNF. However, the mechanisms of how the BDNF levels measured from blood reflect brain BDNF remain unclear. Notably, many factors influence peripheral BDNF levels, and a high inter-individual variability exists in plasma (Lommatzsch et al., 2005) and serum BDNF (Naegelin et al., 2018). The levels of plasma BDNF have been shown to vary within a day and between days, with

highest levels occurring in the morning and a trend of constant decreasing towards the night suggestive of circadian regulation (Begliuomini et al., 2008).

While the connection of brain BDNF with peripheral BDNF is not yet fully elucidated, levels of serum BDNF have been shown to correlate with levels of cortical BDNF in rats (Karege et al., 2002). Electroconvulsive shock has also been shown to alter levels of BDNF-related micro-RNAs (miRNAs) both in rat brains and blood (Ryan et al., 2013). In addition, ECS regulates the expression of many immediate-early genes (IEGs) with specific temporal patterns (Dyrvig et al., 2014). Preclinical evidence has accumulated regarding the neurotrophic effects of ECS in rodents, for which ECS – as well as MAOIs and SSRIs – increased the expression of BDNF in the hippocampus (Nibuya et al., 1995). Similar increases in BDNF levels after ECS in rats have also been observed in other studies. For example, Altar et al. (2003) reported that after 10 daily ECS treatments, BDNF levels were upregulated in the frontal cortex, entorhinal cortex, parietal cortex, hippocampus, striatum, and septum. They noted that BDNF increased gradually in the frontal cortex and hippocampus, with peak responses occurring by the fourth day. Li et al. (2007) also reported an increase of hippocampal BDNF after a 14 day ECS treatment course, accompanied by increases in locomotor activity and decreased immobility in the FST. In addition, O'Donovan et al. (2012) investigated the effects of ultra-brief pulse (UBP) (0.3 ms) and brief pulse (BP) (0.5 ms) ECS in naïve rats and found increases in cell proliferation within the dentate gyrus with BP-treated animals after an ECS course of three treatments a week for 22 days. They also reported an increase in hippocampal BDNF and a lower immobility time in an FST after an BP ECS, while for UBP these results were not statistically significant. Intriguingly, a similar study using the corticosterone model of depression in rats reported the effects of BP and UBP ECS in the FST and the increases in BDNF protein in the hippocampus to be essentially equipotent (O'Donovan et al., 2014). The upregulation of activity-dependent *Bdnf* transcripts along with dendritic spine remodeling have also been reported in a chronic stress model of depression in mice after ECS (Maynard et al., 2018).

The increased expression of BDNF after ECS is thought to regulate diverse molecular actions by binding to its cognate receptor TrkB, a receptor tyrosine kinase that mediates the phosphorylation of tyrosine residues in accompanying proteins (Reichardt, 2006). Once activated by its ligand, TrkB receptors dimerize and become autophosphorylated in their catalytic domains (tyrosine residues 701, 705, and 706), which results in increased kinase activity (Cunningham & Greene, 1998; Middlemas et al., 1994; Segal et al., 1996; Stephens et al., 1994), however, recent evidence indicates that TrkB monomers may also initiate cellular signaling (Zahavi et al., 2018). The activated receptor kinase

leads to further activation of the receptor and to the formation of docking sites for adaptor proteins. In short, tyrosine 515 recruits adaptor proteins Shc and fibroblast growth factor receptor substrate 2 (FRS2) to activate signaling through the Ras – mitogen-activated protein kinase (MAPK, i.e. extracellular signal-regulated kinase ERK) pathway and the phosphatidylinositol 3-kinase (PI3K) – Akt (i.e. Protein kinase B) pathway, while tyrosine 816 is the binding site for phospholipase Cγ (PLCγ) (**FIGURE 3**). Additionally, adaptor proteins may also associate with phosphotyrosine residues in the catalytic domain (for thorough reviews, see Kaplan & Miller, 2000 and Minichiello, 2009).

TrkB-induced activation of downstream pathways orchestrates diverse effects on synaptic plasticity, proliferation, differentiation, and cell survival (Alonso et al., 2004; Gonzalez et al., 2016; Huang & Reichardt, 2003). For example, the MAPK pathway leads to the translocation of p44/42-MAPK into the nucleus and to the further regulation of transcription factors, such as cyclic AMP response element binding protein (CREB) (Patterson et al., 2001; Ying et al., 2002). The activation of the PI3K – Akt pathway leads downstream to the activation of the mammalian target of rapamycin (mTOR) and its downstream effector p70S6 kinase (p70S6k) (Kumar et al., 2005; Takei et al., 2004), further promoting trophic actions and protein synthesis. Akt may also phosphorylate glycogen synthase kinase 3 β (GSK3β) in the serine 9 residue, essentially inhibiting the actions of this promiscuous kinase (Eleonore Beurel et al., 2015). Moreover, the activation of PLCγ activates the enzyme to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol trisphosphate (IP_3), which act as second messengers regulating protein kinase C (PKC) and intracellular Ca^{2+} release leading to the activation of Ca^{2+}/calmodulin (Ca2+/CaM) dependent protein kinases (CaMKK and CaMKIV) (Reichardt, 2006). In particular, this tyrosine 816 mediated signaling appears important for hippocampal synaptic plasticity, since a point mutation of the residue impairs signaling through calcium-dependent protein kinases to CREB (Minichiello et al., 2002).

Since increased BDNF-TrkB signaling has been proposed to be sufficient to explain the effects of traditional antidepressants in rodents (Koponen et al., 2005; Saarelainen et al., 2003; Shirayama et al., 2002; Siuciak et al., 1997), the activation of TrkB may also hold relevance for ECT. Surprisingly, there are not many studies investigating TrkB activation in the preclinical context. One study investigated the total and phosphorylated levels of BDNF receptor TrkB in the rat hippocampus after a 10-day ECS treatment regimen (Enomoto et al., 2017). The study reported an increase in both BDNF levels and $TrkB^{Y706}$ phosphorylation while the total levels of TrkB were downregulated, suggesting ligand-induced downregulation of the receptor. Conversely, in another study,

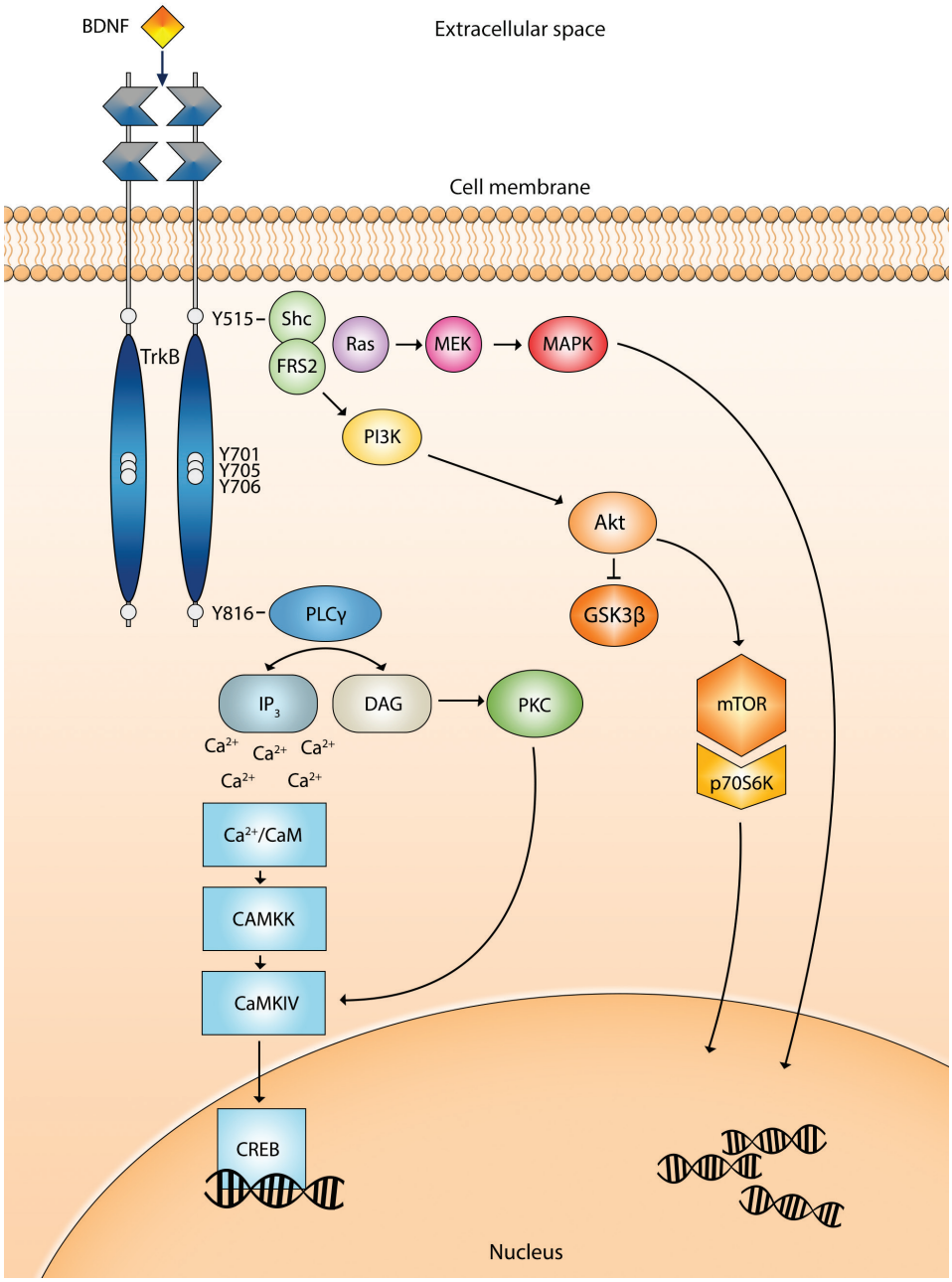

FIGURE 3. Main signaling pathways of the BDNF receptor TrkB. Phosphorylation upon BDNF binding can happen in the catalytic domain (Y701/Y705/Y706), the Shc binding site (Y515), or the PLCγ binding site (Y816). The activated receptor may recruit adaptor proteins to signal through the Ras – MAPK pathway, the PLCγ pathway, and the PI3K – Akt pathway, which lead to diverse cellular changes.

TrkB^{Y706} phosphorylation in the rat prefrontal cortex (PFC) was not found to be regulated acutely by ECS treatment, while p44/42-MAPK signaling was robustly increased (Hansen et al., 2007). Increased MAPK signaling has also been reported by others acutely in the rat hippocampus (HC) (Kang et al., 2002), PFC, cerebellum (Jeon et al., 1998), and after repeated ECS treatments, in the PFC (Kang et al., 2006). In addition, increased phosphorylation (functional inhibition) of GSK3β^{S9} has also been reported after acute ECS in the HC and PFC of mice (Basar et al., 2013) and rats (Roh et al., 2003).

Increased neurogenesis after ECS has been consistently reported in the literature. Madsen et al. (2000) demonstrated neurogenesis in the dentate gyrus of rats treated with 10 ECS seizures, with many of the newborn cells displaying a neuronal phenotype. Moreover, Perera et al. (2007) reported similar effects in adult nonhuman primates. Increased hippocampal neurogenesis has also been observed with ECS after chronic corticosterone administration (Hellsten et al., 2002), and has been reported to be necessary for antidepressant-like behavioral changes in a corticosterone model of depression (Schloesser et al., 2015). Furthermore, Olesen et al. (2017) demonstrated using chronic restraint stress and a clinically relevant ECS schedule in rats that the newly born neurons survive up to 12 months, but are not associated with increases in mobility in the FST. In addition, increases in hippocampal dendritic arborization (Smitha et al., 2014) and the regulation of markers associated with synaptogenesis (Okada-Tsuchioka et al., 2014) have been associated with ECS in rats. These intriguing findings, along with the fact that hippocampal atrophy is present in MDD, may at least partly explain neuroimaging studies showing hippocampal enlargement in humans after ECT (Dukart et al., 2014; Nordanskog et al., 2010; Tendolkar et al., 2013). In a meta-analysis comprising of eight studies with a total of 193 participants, ECT was found to increase volumes of both the hippocampus and the amygdala (Takamiya et al., 2018). These findings have paved the way for the hypothesis of hippocampal enlargement as a potential biomarker for treatment outcome of ECT in severely depressed patients. However, a recent study indicates that hippocampal enlargement in humans does not seem to be associated with the clinical outcome of ECT (Oltedal et al., 2018).

Modern functional imaging technologies have also provided the ability to study brain connectivity. Indeed, abnormalities in the connectivity of neuronal networks have been hypothesized to underlie the mood symptoms of depressed patients (Kaiser et al., 2015; Wang et al., 2012). Three important networks known as the affective network, the cognitive control network, and the default mode network have been proposed to mediate different aspects of the disorder such as decreased focus, rumination, and emotional dysregulation (Sheline et al., 2010). In particular, an fMRI study of depressed patients noted

increased resting state functional connectivity from these three networks to a bilateral dorsal medial prefrontal cortex region and vice versa (Sheline et al., 2010). They suggest that reducing the increased connectivity to this area could be a potential target for the treatment of depression. Moreover, Perrin et al. (2012) investigated the acute effects of ECT on global functional connectivity and found a decrease localized to a limited area within the left dorsolateral prefrontal cortex (DLPFC), an area of the brain previously implicated in depression and cognitive function (Steele et al., 2007). On the other hand, Liu et al. (2015) reported an increase in the local activity and connectivity of the subgenual anterior cingulate cortex (sgACC) and suggested that these changes play a key role in the mechanisms underlying the effectiveness of ECT. Pretreatment connectivity measures of the DLPFC and sgACC have also been proposed to predict ECT treatment outcomes in a recent study (Leaver et al., 2018). Taken together, these results suggest that the therapeutic mechanisms of ECT may include the normalization of hyper- or hypoconnectivity of certain brain networks.

Since prefrontal slowing, diminished cerebral blood flow, reduced metabolism, and altered connectivity are all present during the postictal state of ECT, this state has been suggested to underlie the key mechanism of the action of ECT (Krystal & Weiner, 1999). The findings of increased BDNF expression following seizure activity (Duman et al., 1997) suggest that neurotrophic signaling mechanisms might mediate the possible reactivation or rewiring of diminished connectivity among neuronal networks. Drawing together many studies, Farzan et al. (2014) proposed a connectivity resetting hypothesis of ECT action, which postulates that the therapeutic effects of ECT are mediated through resetting patterns of neural connectivity. They suggest that this resetting takes place through networks such as thalamocortical pathways, which further modulate cortical neuronal oscillations. Importantly, evidence of increased intra- and internetwork connectivity in support of network reconfiguration is emerging (Wang et al., 2018). Many similar changes have also been observed with ketamine, another rapid-acting treatment of depression, as will be discussed in the next chapter.

2.2.2 Ketamine

Ketamine was first synthesized in 1962 by the Parke-Davis pharmaceutical company, following the discovery of phencyclidine (PCP), another arylcyclohexylamine dissociative anesthetic (Denomme, 2018). Due to PCP's unwanted profile of effects, many of its subsequent derivatives were screened in animal experiments by Parke-Davis pharmacologists. From these experiments, ketamine emerged as the lead compound. After animal testing, ketamine was first

given to prisoners in studies led by EDWARD DOMINO and was found to be a safe and short-acting anesthetic in humans. Many of the peculiar psychotropic effects of PCP, however, were still present. Thus, ketamine was coined as a dissociative anesthetic (Domino et al., 1965).

Ketamine is the mixture of two optical stereoisomers: S(+) and R(-)-ketamine. It is pharmaceutically produced in both racemic and enantiopure preparations. Its main pharmacological mechanism of action is the blocking of NMDARs, a key component of glutamatergic excitatory neurotransmission (MacDonald et al., 1991). The enantiomers of ketamine have slightly different effects. S-ketamine is often preferred in clinical anesthesia due to its more potent activity at blocking NMDARs, while R-ketamine has a much lower affinity for NMDARs (Zanos et al., 2018). Based on animal experiments, R-ketamine has been proposed to be the ideal isomer for treatment of depression due to its less pronounced profile of psychotomimetic effects (Yang et al., 2015), however no clinical evidence exists for the superiority of either isomer.

The classical NMDAR antagonists ketamine, PCP, and MK-801 are all non-competitive inhibitors of NMDAR ion channels (Bolshakov et al., 2003; MacDonald et al., 1991). They exhibit a trapping block by entering the ion channel and then being captured inside the closing pore. Some other NMDAR antagonists, such as memantine, are thought to act as partial trapping blockers – only hindering the channel closure but not entirely preventing it (Blanpied et al., 1997). Ketamine has also been proposed to have many other targets, including dopaminergic, serotonergic, adrenergic, opioidergic, cholinergic, and sigma receptors. It also has effects on serotonin, noradrenaline, and dopamine uptake transporters (SERT, NET, DAT respectively) and ion channels, such as voltage-gated sodium channels (VGSC) (Haeseler et al., 2003) and hyperpolarization-activated cyclic nucleotide gated (HCN) channels (Zhou et al., 2013). For a review of ketamine's pharmacology, see Zanos et al. (2018).

Ketamine is rapidly distributed in the body, has low plasma protein binding, and a short elimination half-life of two to four hours (Clements & Nimmo, 1981; Mathew & Zarate, 2016). While (R,S)-norketamine (NK) is the initial metabolite, (2R,6R;2S,6S)-hydroxynorketamine (HNK) and (R,S)-dihydronorketamine (DHNK) are among the major circulating metabolites in human plasma after a typical ketamine infusion used in the treatment of depression (Zarate et al., 2012; Zhao et al., 2012). Peak plasma concentrations are reached in approximately 1.3 hours for NK and 3.8 hours for DHNK and HNK (Zhao et al., 2012). Plasma levels of HNK and DHNK are still significantly elevated 24 hours after the infusion and can be detected for up to 48 hours in some patients. The initial N-demethylation to NK is mainly catalyzed by liver cytochrome P450 enzymes CYP2B6 and CYP3A4, followed by hydroxylation into

hydroxynorketamines and dehydronorketamine (Portmann et al., 2010). Several minor metabolic pathways also exist (Adams et al., 1981; Woolf & Adams, 1987). Ketamine's metabolism and pharmacokinetics are reviewed thoroughly by Zanos et al. (2018).

The dissociative anesthesia produced by ketamine is different from many other sedatives and anesthetics as it is not a sedative or a hypnotic drug (Sinner & Graf, 2011). Ketamine-induced blockade of NMDARs leads to the occurrence of dissociative states, where patients may experience being conscious while being drawn away from their sensory perception (Mathew & Zarate, 2016). The level of dissociation is dose-dependently increased, with higher doses deepening into hallucinatory-like states of open and closed-eye visuals and extreme perturbations of thought and bodily sensation (Garfield et al., 1972). Patients going through ketamine anesthesia often report dream-like states unlike anything experienced previously, such as sensations of traveling through space and time while being detached from bodily sensation. Anesthetic doses induce a state of total dissociation often accompanied by amnesia, since NMDARs are crucial components of long-term potentiation and memory formation. Some of these psychoactive properties of ketamine have been sought by recreational users, as evidenced by the surge in recreational use in the 1970s that continues to this date (Mathew & Zarate, 2016).

Due to its unique mechanism of action, ketamine is also considered to be safe for emergency anesthesia in a prehospital setting. The dosing range is relatively wide, and ketamine supports cardiovascular function due to its sympathomimetic action, maintains respiratory function, and provides effective analgesia comparable to morphine (Marland et al., 2013). Following its Food and Drug Administration (FDA) approval in the 1970s, these properties prompted the use of ketamine on American soldiers during the Vietnam War. Today, ketamine is often employed in emergency units for anesthesia and widely used for procedural sedation in a variety of patient populations, from children to adults (Sinner & Graf, 2011). Ketamine is not preferred for general anesthesia performed at hospitals due to its potent psychotropic effects and the potential to produce emergence phenomena, manifesting as profound confusion or hyperexcitation upon waking up from the dissociative state in up to 20% of adults (Marland et al., 2013). However, these side-effects of ketamine were desirable in the psychiatric investigations in the 1970s, which consisted of using ketamine as an "abreactive agent." A variety of doses more than capable of producing psychotropic experiences were employed in early trials (Khorramzadeh & Lotfy, 1973). While intriguing anecdotes of facilitated psychotherapeutic responses in psychiatric patients were described, it took close to three decades before the first scientifically rigorous investigations were launched.

Berman et al. (2000) were the first to demonstrate the rapid-acting antidepressant effects of ketamine in patients suffering from MDD. These results have since been replicated in several clinical trials (Lapidus et al., 2014; Murrough et al., 2013; Zarate, Singh, Carlson, et al., 2006). Ketamine's effects take place within hours of drug administration and these effects may last for days or weeks after a single dose. In addition, the antidepressant-like effects of ketamine have been demonstrated in various animal models (Autry et al., 2011; Li et al., 2011; Maeng et al., 2008). However, the psychoactive properties and abuse liability of ketamine have hindered its widespread clinical application in treating depression (Krystal et al., 1994). Perhaps partly due to the stigma associated with hallucinogenic drugs, research on ketamine has been mostly focused on utilizing the lowest possible doses with minimal psychoactive effects. A large interest also exists in developing treatments that mimic the action of ketamine without its psychotropic side effects. While preclinical and clinical investigations have figured out many of the effects that ketamine has in the brain, the precise neurobiological basis of its rapid antidepressant effects remains a mystery.

2.2.2.1 Clinical administration of ketamine

Doses of ketamine in the induction of anesthesia are typically in the range of 1 to 2 mg/kg intravenously, which produce dissociative anesthesia within one to two minutes of injection (Marland et al., 2013). When ketamine is used for the treatment of depression, intravenous doses from 0.1 to 0.5 mg/kg are commonly employed (Andrade, 2017). The first randomized controlled trials demonstrating ketamine's efficacy used an IV dose of 0.5 mg/kg over 40 minutes (Berman et al., 2000; Zarate, Singh, Carlson, et al., 2006). This dosage and route of administration have been adopted by many clinicians since. According to C. Zarate, ketamine is typically administered in research settings during the morning for convenience (personal communication, 23.11.2018). The peak of antidepressant effects occurs 24 hours after an infusion, but most patients experience a relief of their depressive symptoms within two to four hours of administration. Dissociation is variably present during the infusion, but most patients can still answer questions. Once the 40-minute infusion ceases, the patients are for the most part neither in sedation or stimulation states, but are more talkative and active, as in a non-depressed state (C. Zarate, personal communication 23.11.2018).

Ketamine can be administered orally, sublingually, intranasally, intramuscularly, and subcutaneously, but best bioavailability is achieved by intravenous or intranasal administration (Andrade, 2017). Notably, a recent open longitudinal study suggested that a rapid ketamine bolus of 0.5 mg/kg also has rapid antidepressant effects (Vidal et al., 2018). Recent clinical trials also indicate the antidepressant action of intranasal (Daly et al., 2018; Lapidus et al., 2014) and

per oral (Arabzadeh et al., 2018; Domany et al., 2018) ketamine administration. In clinical practice, ketamine treatments can be repeated and dosages can be increased if patients do not respond to initial administration (Andrade, 2017). Consecutive sessions may be also used to extend and maintain antidepressant effects.

A typical course of experimental ketamine treatment in the Turku University Hospital in Finland consists of a psychiatric evaluation, electrocardiogram (ECG) and blood pressure measurements, and urine and plasma screenings before the initiation of treatment (Taiminen, 2017). Racemic ketamine is then continuously infused at a dose of 0.5 mg/kg over 40 minutes. Blood pressure is constantly monitored during the ketamine infusion and the patient is kept in the hospital for at least four hours after the treatment. If the treatment response is evident, the patient may receive additional treatments twice a week for a period of one to two weeks. Treatment can be then continued for up to three months with ketamine infusions once a week. During the course of the treatment, ECG, blood pressure, and screenings are checked monthly.

Despite the widespread use of ketamine in clinical practice, the safety of long-term ketamine administration remains a continuing concern. Ketamine impairs memory function acutely, and may cause prolonged memory problems when used in high doses for longer periods of time (Morgan & Curran, 2006). While the findings of JOHN OLNEY in the 1980s were suggestive of NMDAR antagonist-induced neurotoxicity (Olney et al., 1989) – so-called Olney's lesions in rodents – neurotoxicity in primates likely requires significantly higher doses. However, neuroimaging studies of chronic ketamine users have indicated cortical atrophy and reductions in prefrontal gray matter after two to four years of ketamine abuse (Liao et al., 2011; Wang et al., 2013). Notably, the majority of the subjects in the Wang et al. study were using 1 g of ketamine a day – far beyond the dosage range used in the treatment of depression or even in anesthesia. Cognitive deficits have also been observed in users who used ketamine more than four times a week (Morgan et al., 2010). Since there are no reports of ketamine anesthesia-induced neurocognitive deficits despite its widespread use, it is likely that ketamine produces significant neurotoxicity only after chronic administration of very high doses. The safety and tolerability of long-term ketamine treatments for depression thus must be carefully studied.

2.2.2.2 Research on the mechanisms of ketamine

Since the breakthrough clinical trial of Berman et al. (2000) reporting the rapid-antidepressant effects of a single continuous infusion of 0.5 mg/kg ketamine over 40 minutes in treatment-resistant patients, most studies have followed along similar dosages of ketamine (Diazgranados et al. 2010, Valentine et al.

2012, Murrough et al. 2013). These sub-anesthetic dosages at slow rates of infusion are described to produce only minor psychoactive effects, avoiding the more psychedelic states produced by higher but still sub-anesthetic dosages. Similar treatment outcomes have also been observed with a single intranasal administration of 50 mg of ketamine (Lapidus et al. 2014). The potential of intranasal ketamine has also been investigated by Janssen in their clinical trial comparing the effects of 28, 56, and 84 mg doses of S-ketamine (Daly et al. 2018). Interestingly, this study found that the higher doses produced a longer-lasting remission of depressive symptoms. In addition to its antidepressant effects, intranasal administration of S-ketamine (84 mg) has also been reported to reduce suicidality in patients at imminent risk for suicide (Canuso et al., 2018). Most importantly, in a recent double-blind active placebo-controlled trial of various subanesthetic ketamine doses, only the higher doses of 0.5 mg/kg and 1.0 mg/kg were found to have clinically meaningful effects (Fava et al., 2018).

While impressive numbers of individual trials have investigated the efficacy of ketamine in treating MDD, the literature still lacks solid evidence for dose-dependent effects or the minimum effective dosage for achieving antidepressant responses. The practice of using low doses of ketamine in treating depression seems sensible if the psychedelic or dissociative effects intervene with the antidepressant outcome, but evidence for this is lacking. On the contrary, some studies suggest that the opposite could be true. For example, Loo et al. (2016) investigated the effects of ketamine dose titration in depressive patients with intravenous, intramuscular, and subcutaneous routes of delivery. The placebo-controlled pilot trial consisted of 15 patients, with ascending doses rather than randomized design. They found no differences between methods of administration, but the dose required for the antidepressant response differed between individuals, suggesting that dose titration should be done on an individual basis. A higher dose resulted in greater antidepressant response as well as greater psychotomimetic effects. These results are also in line with a meta-analysis by Xu et al. (2016), who performed a systematic review and meta-analysis of nine trials with ketamine. Six trials were categorized as a low dose (0.5 mg/kg IV) and three trials tested a very low dose of ketamine (one 50 mg intranasal spray, one 0.1-0.4 mg/kg IV and one 0.1-0.5 mg/kg IV or SC). They reported that a low dose of ketamine appears to be more effective than a very low dose, but that there is substantial heterogeneity in the clinical response, with one-fifth of patients showing remission of symptoms at one week, but most others showing benefits that were not as enduring. Additionally, Lai et al. (2014) compared different doses (0.1, 0.2, 0.3, 0.4 mg/kg) of ketamine administered to four patients as an IV infusion over five minutes in a dou-

ble-blind, placebo-controlled, crossover design. They presented dose-response data of both ketamine efficacy and psychoactive effects and proposed that antidepressant efficacy may be dose related, and that psychoactive effects were dose-related.

Some trials have reported evidence that points towards the importance of dissociative or psychoactive effects in producing concurrent antidepressant responses. For example, a double-blind, cross-over, placebo-controlled clinical trial by Sos et al. (2013) found a substantial relationship between the antidepressant response and the psychotomimetic effects elicited by ketamine treatment. Their trial shows that more intense psychotomimetic symptoms (as assessed by the Brief Psychiatric Rating Scale (BPRS)) correlated with improved mood ratings on the Montgomery-Åsberg Depression Rating Scale (MADRS) seven days post-ketamine infusion. Luckenbaugh et al. (2014) investigated whether the psychoactive effects of ketamine are important to the subsequent antidepressant effects. They analyzed 108 treatment-resistant depressive patients from three studies, of which two were double-blind and the third had an open-label design. In these studies patients received a single subanesthetic dose (0.5 mg/kg) of ketamine via an intravenous infusion over 40 minutes. Ratings of depression, hypomania, mania, psychotomimetic, and dissociative symptoms were measured using the Hamilton Depression Rating Scale (HDRS), the Young Mania Rating Scale (YMRS), the BPRS, and the Clinician Administered Dissociative States Scale (CADSS). Psychiatric ratings were collected before and at 40, 80, 110, and 230 minutes after the start of infusion, and at various time points post-infusion. The correlation of increased CADSS at 40 minutes and improvement in HDRS at 230 minutes and on day seven were found to be significant. However, changes in YMRS, BPRS total, or BPRS positive symptoms at 40 minutes were not found to be correlated with the improvement of HDRS. Luckenbaugh et al. concluded that the present correlation suggests that dissociative side effects may serve as a clinical biomarker to predict ketamine's efficacy. Most recently, a study reported that dissociative symptoms measured by the CADSS were found to be related to the antidepressant responses after 0.5 mg/kg of ketamine (Niciu et al., 2018). However, contrasting results have also been published that show no correlation between maximum CADSS and HDRS responses at any time following ketamine infusion (Valentine et al., 2011).

Some researchers have proposed that the antidepressant effects cannot be separated from the dissociation and/or psychedelia, and that these are central to successful treatment when combined with psychotherapy (Wolfson 2014). An intriguing recent clinical trial, however, demonstrated that the antidepressant effects of ketamine can be attenuated with the administration of an opioid

receptor antagonist naltrexone, while the dissociative effects are still present (Williams et al., 2018). However, the small number of patients in this trial limit the possibility of making thorough conclusions.

Preclinical studies of ketamine have focused on identifying important neuronal, molecular, and metabolic targets of ketamine. The first preclinical work suggesting antidepressant-like action of NMDAR antagonists in the FST was done by Trullas and Skolnick (1990) in mice. They demonstrated that the competitive NMDA antagonist AP-7 and non-competitive antagonist MK-801 both reduced the immobility of animals subjected to the FST, similar to the tricyclic antidepressant imipramine. Following these findings, Skolnick et al. (1996) demonstrated that chronic antidepressant treatments change radioligand binding to NMDARs in the cerebral cortex and proposed NMDARs as a common pathway for traditional antidepressant action. Additional evidence for the rapid-antidepressant behavioral effects of ketamine, MK-801, and Ro25-6981, a selective antagonist for the NMDAR subtype 2B (NR2B), have since been published (Maeng et al., 2008). Ketamine, however, was found to produce the most sustained responses.

Since NMDARs are crucial mediators of excitatory glutamatergic neurotransmission, one could expect their inhibition to lead to decreased neuronal excitability. Intriguingly, among one of the most prevailing hypotheses of ketamine's antidepressant action is the disinhibition hypothesis, which proposes that ketamine's antidepressant action is due to the preferential inhibition of NMDARs present in gamma-aminobutyric acid (GABA) producing interneurons, leading to decreased inhibition of excitatory pyramidal neurons and increased glutamatergic signaling at subanesthetic doses in rodents (**FIGURE 4**) (Homayoun & Moghaddam, 2007; Moghaddam et al., 1997). Another proposed cellular hypothesis of ketamine's action revolves around the direct antagonism of extrasynaptic NMDARs present on pyramidal neurons, which disrupt the tonic activation of NMDARs by ambient glutamate and trigger homeostatic synaptic plasticity alterations and compensatory increases of excitatory drive in the prefrontal cortex (Miller et al., 2016). In particular, these changes are thought to be mediated by the blockade of extra-synaptic NMDARs containing NR2B subunits (Miller et al., 2014). Ketamine has also been proposed to inhibit spontaneous NMDAR-mediated miniature excitatory post-synaptic currents (mEPSCs) and to trigger increases in the translation of proteins such as BDNF by reducing the phosphorylation of eukaryotic elongation factor-2 (eEF2), leading to antidepressant-like effects (Autry et al., 2011; Nosyreva et al., 2013; Sutton et al., 2007). In addition, decreased activation and burst firing of neurons in the lateral habenula after ketamine administration has been associated with acute antidepressant effects in congenitally helpless rats, which

otherwise display abnormal NMDAR-dependent firing and helpless behavior (Yang et al., 2018). These hypotheses, however, do not exclude each other, and might all be contributing to the molecular alterations seen after ketamine administration.

The excitatory effects of ketamine seem to be very dose dependent, with anesthetic doses of 200 mg/kg intraperitoneally (IP) administered decreasing acute glutamate activity measured by microdialysis in rats and lower doses of 10, 20, and 30 mg/kg increasing glutamate outflow in the prefrontal cortex (Moghaddam et al., 1997). Ketamine has been also shown to provoke transient changes in glutamate cycling in the medial prefrontal cortex (mPFC) of rats (Chowdhury et al., 2017). This surge in glutamate after ketamine administration has been proposed to underlie the rapid-acting antidepressant effects, perhaps via the regulation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPARs), since AMPAR blockade with NBQX abolishes antidepressant-like behavioral responses in mice and rats (Koike & Chaki, 2014; Koike et al., 2011; Maeng et al., 2008). Moreover, positive allosteric modulators of AMPARs produce antidepressant-like behavioral effects in rodents (Knapp et al., 2002; Li et al., 2001) and increase the synthesis of BDNF (Lauterborn et al., 2000; Mackowiak et al., 2002).

Rapid synaptic neurotransmission in the brain is mediated by AMPARs, which are ionotropic transmembrane glutamatergic receptors (Derkach et al., 2007). These receptors play a key role in the regulation of activity-dependent changes in the synaptic strength of excitatory synapses and are involved in numerous complex signaling pathways that regulate synaptic plasticity. AMPARs are constantly in dynamic motion to and from the postsynaptic membrane. NMDAR activation and the following Ca^{2+} influx is thought to play a role in the lateral diffusion and incorporation of GluR1 subunit containing AMPAR from extrasynaptic sites to the synapses thus promoting synaptic potentiation. Small GTPases Ras and Rap have been found to control AMPAR trafficking and synaptic potentiation through mechanisms requiring p44/42-MAPK activation (Zhu et al., 2002). Moreover, p44/42-MAPK is downstream of Ras/MEK (MAPK/ERK kinase), which is downstream of Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK). CaMKK is sensitive to Ca^{2+} elevation, providing a putative route of signaling for early long-term potentiation (e-LTP) expression (Derkach et al., 2007; Schmitt et al., 2004). The late phase of LTP (L-LTP) also requires changes in the transcription of genes and the synthesis of new proteins (Derkach et al., 2007). Among these proteins are proposedly AMPAR subunits and other components involved in regulating their movement. Additionally, many proteins important for the structural changes in dendritic spines are thought to be produced, perhaps via the translocation

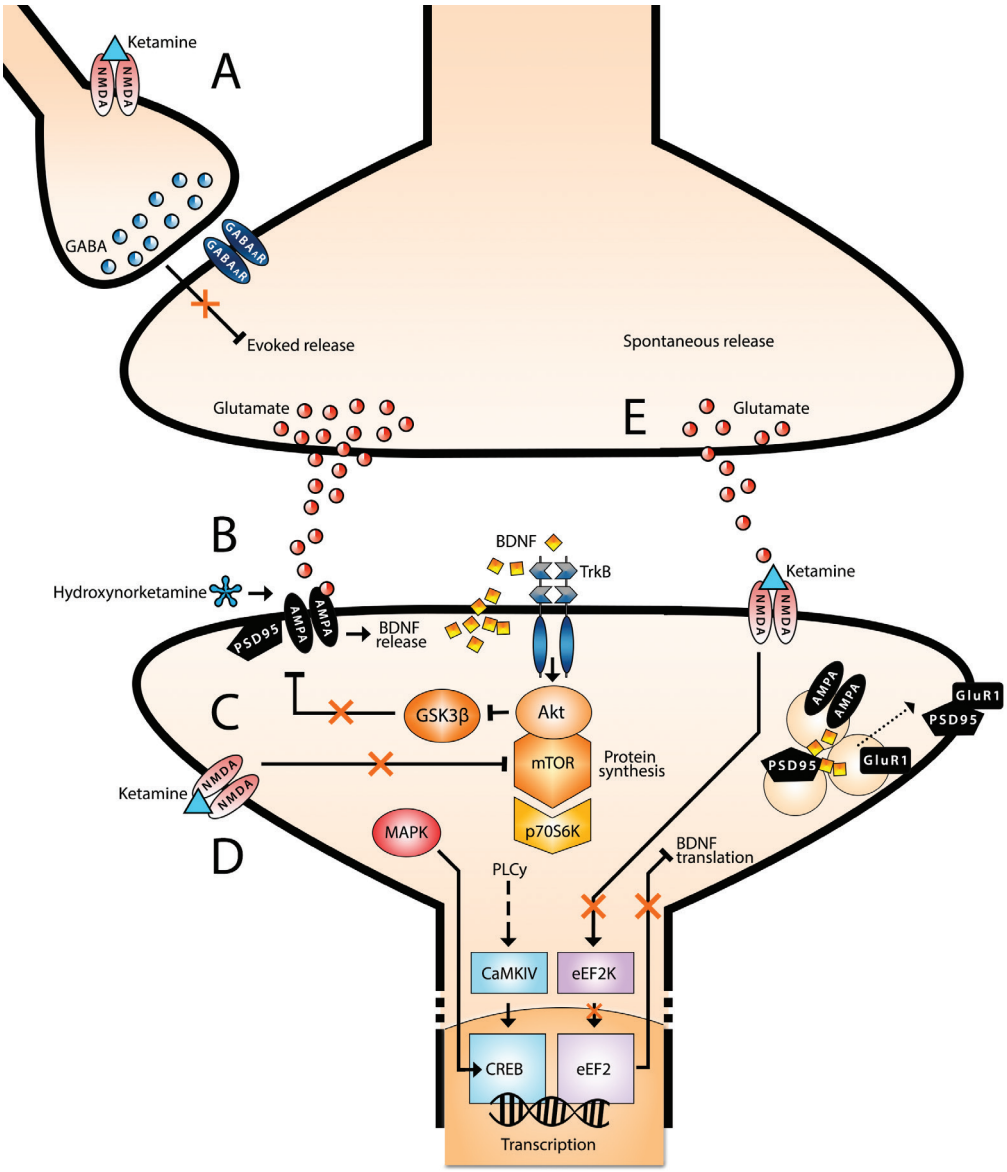

FIGURE 4. Overview of proposed molecular mechanisms underlying ketamine's rapid antidepressant action. (A) Disinhibition hypothesis: ketamine blocks NMDARs on GABAergic inhibitory interneurons, which leads to decreased inhibitory tone on excitatory pyramidal neurons. Increased glutamate release acts on postsynaptic AMPARs and induces cellular effects, e.g. BDNF release, TrkB activation, and the regulation of downstream pathways important for plasticity and protein synthesis, including the activation of MAPK and mTOR and the regulation of AMPAR dynamics and scaffolding proteins like PSD95. (B) Hydroxynorketamine metabolites modulate postsynaptic AMPAR signaling leading to downstream changes. (C) The inhibition of GSK3β by ketamine reduces phosphorylation of $PSD95^{T19}$, which augments AMPAR signaling by reducing the internalization of AMPAR subunits. (D) Ketamine blocks extrasynaptic NMDARs that are normally tonically activated by glutamate and disinhibits mTOR activity. (E) The blockade of spontaneous NMDAR-mediated neurotransmission leads to the disinhibition of BDNF translation via eEF2-dependent mechanisms.

of polyribosomes from dendritic shafts into spines for local translation (Ostroff et al., 2002).

Among other important molecular targets, the inhibition of GSK3β by ketamine via the phosphorylation of Ser9 residue has been suggested to be necessary for the rapid antidepressant-like effects observed in mice (Beurel et al., 2011). This inhibition can take place through Akt (Zhou et al., 2014) and reduces the phosphorylation of postsynaptic density protein 95 (PSD-95) Thr19 residue, which augments AMPAR-mediated signaling by diminishing the internalization of GluA1 subunits (Beurel et al., 2016). Inhibition of GSK3 has also been shown to potentiate the synaptogenic and antidepressant-like effects of a subthreshold dose of ketamine in rats (Liu et al., 2013). However, contradictory results by Ma et al. (2013) failed to demonstrate long lasting-antidepressant effects of a GSK3β inhibitor in a model of chronic stress in mice. Importantly, GSK3β is a promiscuous kinase with multiple targets and the precise mechanisms of its regulation are difficult to ascertain (Li & Jope, 2010).

Molecular investigations into the intracellular effects of ketamine in rats have revealed the rapid regulation of the mammalian target of rapamycin (mTOR) pathway as an important molecular alteration. The mTOR is particularly important for cellular protein synthesis, along with increased synaptic protein levels and the formation of spines in the prefrontal cortex after small doses of ketamine (5-10 mg/kg, IP) (Li et al., 2010). In this study, phosphorylation changes were observed within 30 minutes in mTOR, 4E-BP1, ERK1/2, Akt, and p70S6K proteins in isolated synaptoneurosomes, while synaptic proteins Arc, Synapsin I, PSD95, and GluR1 were upregulated after two hours. In addition, the blockade of mTOR activity using rapamycin (ICV) abolished the effects of ketamine on synaptogenesis and in behavioral assays, suggesting these changes are dependent on mTOR-driven protein synthesis. Li et al. (2010) also reported that, unlike a dose of 10 mg/kg, 80 mg/kg of ketamine failed to reduce immobility time in the FST. These results further support the idea of a specific dosage range of ketamine in promoting acute glutamatergic excitability and the subsequent intracellular effects required for antidepressant-like effects. Based on the current evidence, it is likely that ketamine not only exerts differential dose-dependent effects on neuronal activity, but also temporally varying effects.

Some studies have pinpointed the actions of ketamine on the infralimbic prefrontal cortex (IL-PFC) in rodents. For example, the inactivation of IL-PFC using muscimol has been demonstrated to block the antidepressant-like behavioral actions of ketamine, while a microinfusion of ketamine to the IL-PFC essentially recapitulated the effects of systemic ketamine administration (Fuchikami et al., 2015). Moreover, optogenetic stimulation of the IL-PFC

produced rapid and sustained antidepressant effects that were associated with increases in the number and function of spines. The authors highlight the importance of neuronal activity in producing ketamine's effects. Moreover, the latest research has also implicated a subtype of pyramidal neurons in the antidepressant effects of ketamine. The study assessed *Drd1* and *Drd2* dopamine receptor-expressing pyramidal neurons and found that the optogenetic activation of *Drd1* pyramidal cells of the mPFC produced rapid and long-lasting antidepressant effects, while *Drd2* neuron stimulation was ineffective (Hare et al., 2019).

To make things more complicated, it may be that the regulation of molecular events important for antidepressant-like effects cannot deduced from the effects of ketamine alone. Notably, recent study by Zanos et al. (2016) demonstrated that the ketamine metabolite HNK was sufficient to promote rapid antidepressant-like responses in mice, and that the metabolism of ketamine to HNK was required for these responses. They suggested these effects of HNK may be independent of NMDAR inhibition, involving a more direct activation of AMPARs instead. Moreover, (2R,6R)-HNK was proposed to act as the more potent enantiomer in exerting antidepressant-like effects on a behavioral and molecular level. The authors further support this hypothesis with the previous findings that R-ketamine is more potent than S-ketamine in mouse models of depression, and that the antidepressant effects of S-ketamine are not sustained over 24 hours. Moreover, in this study, MK-801 did not exert sustained antidepressant-like effects in mice, which could be argued to be due to the lack of active metabolites. Furthermore, they demonstrated that a deuterated ketamine analogue, that is minimally metabolized into HNK, did not produce ketamine-like behavioral effects. Consistent with the idea of AMPAR activation driving the antidepressant-like effects, the blockade of AMPAR with NBQX prevented both the acute and sustained antidepressant-like behavioral effects of (R,S)-ketamine and (2R,6R)-HNK and ameliorated the acute increase of EEG gamma oscillations (Zanos et al., 2016). Since HNK did not seem to produce the unwanted psychotropic effects of ketamine, this study immediately gained enormous attention.

Controversy around this hypothesis was also imminent, as evidenced by the correspondence of Collingridge et al. (2017). In their letter to the editor, they dispute the idea of NMDAR-independent antidepressant effects of ketamine and bring up various translational problems in interpreting findings from animal models to humans. According to their letter, S-ketamine has been estimated to be around two times as potent as racemic ketamine in humans, citing a clinical trial by Singh et al. (2016). Although this study does not directly compare the ketamine isomers, Singh et al. demonstrated around two weeks

of sustained antidepressant effects after S-ketamine administration, contrary to the effects seen in mice by Zanos et al. (2016). Since S-ketamine is unlikely to be metabolized into (2R,6R)-HNK, Collingridge et al. (2017) conclude that these observations are consistent with NMDAR antagonism as the principal mechanism of action. Moreover, Collingridge et al. underline that comparing ketamine with MK-801 is difficult, since they possess different properties in blocking the NMDARs, and that the therapeutic effects of NMDAR antagonists seem to be associated with their affinity and voltage dependence. This is also evidenced by memantine, which binds with a low affinity and has not been demonstrated to function as an antidepressant in humans. Following the findings of Zanos et al. (2016) on the NMDAR-independent antidepressant actions of HNK, Suzuki et al. (2017) published a study where they assessed NMDAR-mediated mEPSCs in cultures of hippocampal neurons. Most importantly, they demonstrated that (2R,6R)-HNK does indeed inhibit synaptic NMDARs and triggers the phosphorylation of eEF2 similarly to ketamine. However, they also suggest that these ketamine metabolites may explain the sustained antidepressant effects of ketamine, which some other NMDAR antagonists are lacking. Many questions, however, remain unanswered regarding the molecular alterations ketamine induces in animal models and how these changes are connected to its antidepressant effects in humans.

Human brain imaging studies have demonstrated normalized global functional connectivity after subanesthetic ketamine treatment (Abdallah, Averill, Collins, et al., 2017; Abdallah, Averill, Salas, et al., 2017) and changes in the balance of frontoparietal connectivity patterns (Muthukumaraswamy et al., 2015). A recent double-blind, placebo-controlled crossover study used fMRI to demonstrate that connectivity between the insula and the default mode network (DMN) was normalized in MDD patients when compared to healthy controls two days post-ketamine infusion (Evans et al., 2018). Furthermore, this change was reversed after 10 days, in line with the duration of ketamine's antidepressant effects. Evans et al. (2018) used a triple network model of connectivity dysfunction between the DMN, salience (SAL), and central executive (CEN) networks as their working model, which has been suggested to be the cornerstone of psychiatric and neurological disorders, including depression (Menon, 2011). This hypothesis proposes that in MDD, the activity of the DMN is increased (Hamilton et al., 2015), while activity in the SAL and CEN networks are reduced (Menon, 2011). The DMN is a network implicated in introspective thought and ruminative thought patterns, while SAL mediates salient information processing from the outside world and CEN is important in working memory function and attentional processes. Since the insula is involved in the integration of external emotional stimuli and processing of exter-

nal information, the authors suggest increased connectivity between the insula and DMN after ketamine may suggest an improved ability to process external stimuli and thus the improvement of symptoms (Evans et al., 2018).

The effects of ketamine may also vary depending on the baseline conditions of the subjects, since ketamine has been reported to have distinct electrophysiological – as measured by magnetoencephalography – and behavioral effects when given to depressed or healthy subjects (Nugent et al., 2017). While MDD patients show rapid improvements in depressive symptoms, healthy controls may display increases in depressive symptoms for up to a day after ketamine administration. Additionally, Nugent et al. (2017) reported that MDD patients who had lower baseline gamma power but displayed high gamma power after ketamine administration responded better to the treatment. These increases in gamma power lasted for up to nine hours post-ketamine infusion in both healthy controls and MDD patients, suggesting changes in synaptic plasticity that greatly outlast the infusion period. Furthermore, the authors propose gamma power as a potential marker of synaptic homeostasis. In support of the idea that baseline conditions affect the outcomes of ketamine treatments, mice have been found to elicit glutamate functional hyperconnectivity in the chronic social defeat model of depression (McGirr et al., 2017). Administration of subanesthetic ketamine to these mice resulted in large global cortical glutamate transients. Similar effects were observed in naïve mice that were subjected to local cortical inhibition of glutamate transporters and subsequently given ketamine, suggesting a unique sensitivity to subanesthetic ketamine after chronic social defeat stress.

Clinical evidence indicates that the metabolic activity of the prefrontal cortex is increased in healthy volunteers after subanesthetic ketamine administration (Breier et al., 1997). Similarly, increased glutamate neurotransmission in the prefrontal cortex of healthy and depressed patients has been reported after the patients received ketamine (Abdallah et al., 2018; Li et al., 2016). Intriguingly, in rats, ketamine doses up to 60 mg/kg produce behavioral arousal and increase theta range EEG activity but show no activation of the sleep-promoting nuclei of the ventrolateral preoptic nucleus (VLPO) of hypothalamus, as measured with Fos immunoreactivity (Lu et al., 2008). Instead, ketamine was found to activate subcortical wakefulness-promoting nuclei. In the same study, animals that were administered a high dose of 150 mg/kg of ketamine showed signs of hyperarousal upon awakening. Furthermore, two hours after ketamine administration, the expression of Fos in the cerebral cortex, arousal systems, and VLPO were reported to be similar as with the lower dosages that were arousal-promoting. This arousal-promoting effect of NMDA antagonists is followed by a subsequent period of rebound sleep with markedly increased

delta frequency power in rats (Campbell & Feinberg, 1996; Feinberg & Campbell, 1995). Intriguingly, increased slow-wave activity (SWA) has been reported in humans during sleep following subanesthetic ketamine administration, and this has been proposed to predict the therapeutic efficacy of the treatment (Duncan, Sarasso, et al., 2013). In addition to increases in slow EEG oscillations, baseline delta-sleep ratios have also been implicated in rapid antidepressant responses after ketamine (Duncan, Selter, et al., 2013).

The mechanistic link between increased neuronal excitability and the induction of increased slow EEG activity remains unclear. However, the phenomena of increased SWA after prolonged sleep deprivation (Huber et al., 2000) or somatosensory stimulation (Kattler et al., 1994) has been reported in mice and also in humans after rTMS (Huber et al., 2007) or ECT (Sackeim et al., 1996). Combining the variety of known effects of ketamine on synaptic plasticity processes, functional connectivity changes, neuronal metabolism, and the regulation of sleep and wakefulness are instrumental in understanding ketamine's multifaceted profile of effects.

2.2.3 Other putative treatments

Emerging evidence supports the idea that multiple drugs besides ketamine may possess rapid-acting antidepressant potential. The close association between ECT-induced post-seizure neuronal inhibition and its therapeutic efficacy (Fink & Kahn, 1957) encouraged researchers a few decades ago to test the antidepressant actions of isoflurane anesthesia in depressive patients (Langer et al., 1985). Isoflurane is a potent volatile halogenated ether general anesthetic. Its mechanism of action is not entirely known, but it appears to modulate both NMDARs and GABARs among other targets (Jones et al., 1992; Krasowski & Harrison, 2000; Ming et al., 2001). Isoflurane anesthesia deep enough to provoke burst suppression EEG patterns has been demonstrated to produce antidepressant effects comparable to those of ECT in double-blind (Langer et al., 1995, 1985; Weeks et al., 2013) and open-label study designs (Engelhardt et al., 1993). These effects seem to take place relatively rapidly after the first treatment. Isoflurane has also been demonstrated to produce antidepressant-like behavioral effects in animal models of depression and to activate signaling pathways relevant to the antidepressant-like effects of ketamine in mice (Antila et al., 2017; Brown et al., 2018). In particular, isoflurane has been shown to activate TrkB and mTOR signaling while inhibiting GSK3β activity (Antila et al., 2017). Moreover, isoflurane was demonstrated to facilitate LTP in the hippocampus, to increase the activity of parvalbumin interneurons, and to facilitate GABAergic neurotransmission. These changes appeared 24 hours after anesthesia.

Propofol is another general anesthetic that engages NMDARs and GABARs and has been reported to produce rapid-antidepressant effects comparable to ECT in a small open label trial (Mickey et al., 2018). The antidepressant effects of anesthetic doses of propofol used in this study (9-20 mg/kg) appeared to be both rapid and sustained. Like ketamine, propofol is also widely used in lower doses for procedural sedation, and has a rapid onset and offset of action combined with an acceptable safety profile (Lamperti, 2015). Notably, propofol produces dose-dependent decreases in cortical activity similar to isoflurane (Pilge et al., 2014). Further studies are required to validate the putative antidepressant effects of propofol, including possible dose-dependent effects, and to elucidate the molecular changes that take place in the brain during and after propofol anesthesia.

The effects of another anesthetic, nitrous oxide (N_2O), were investigated in a psychiatric context already decades ago. In a study conducted by Brill et al. (1959), schizophrenic and depressive patients received either ECT, ECT and succinylcholine, ECT and thiopental, thiopental alone, or N_2O alone. The authors noted that all treatments contributed to symptomatologic improvement, however, the low sample sizes did not allow for statistical significance. More recently, a mixture of 50% N_2O and 50% O_2 was given to patients suffering from treatment-resistant depression in a small blinded placebo-controlled crossover trial (Nagele et al., 2015). The subjects inhaled the gas for 1 hour and depressive symptoms were measured at 2 hours and 24 hours post-inhalation. Nitrous oxide produced a marked and rapid alleviation of depressive symptoms in some patients when compared to a placebo. Nitrous oxide is also regularly used in procedural sedation and as an additive to more potent anesthetics. Its minimum alveolar anesthetic concentration (MAC) is estimated to be 1.04 atm in humans (Hornbein et al., 1982) and even greater in rats (Gonsowski & Eger 2nd, 1994). Due to this, N_2O is rarely used as a sole anesthetic, but instead often combined with other, more potent general anesthetics such as isoflurane or sevoflurane.

Nitrous oxide is known to act as an NMDAR antagonist (among other targets) similar to ketamine (Mennerick et al., 1998; Yamakura & Harris, 2000), but the intracellular neuronal mechanisms triggered by nitrous oxide treatment remain relatively unstudied. Notably, the molecular effects of N_2O have not been investigated in the context of depression. Nitrous oxide administration at subanesthetic concentrations produces dissociative and psychotropic effects relatively similar to other dissociative anesthetics (Block et al., 1990; Ghoneim, 2001). Moreover, N_2O has been shown to induce cell proliferation in the dentate gyrus of rat hippocampi, similar to ketamine, which is suggestive of neurogenesis (Chamaa et al., 2018). Notably, N_2O is known to paradoxically regulate

slow EEG oscillations in humans by blunting slow EEG activity during administration (unlike other anesthetics) and causing prominent rebound increases in slow EEG activity after the cessation of the gas flow (Foster & Liley, 2011, 2013; Henrie et al., 1961; Williams et al., 1984). Some studies also report increases in higher frequency EEG oscillations during gas inhalation (Rampil et al., 1998). One proposed mechanism for the cortical activation during N_2O treatment may be the increased release of noradrenaline in the cerebral cortex (Yoshida et al., 2010). However, the relationship of these neurobiological effects to their putative antidepressant potential is unknown.

The antimuscarinic agent scopolamine has been shown to produce antidepressant effects in small randomized placebo-controlled clinical trials (Drevets & Furey, 2010; Furey & Drevets, 2006). In these trials, scopolamine hydrobromide was administered as an intravenous infusion of 4 μg/kg. Significant clinical responses were observed three to four days after the first treatment, suggestive of a slightly slower onset of antidepressant effects compared to ketamine. These responses have been reported to last for more than two weeks after the final treatment. However, in a recent randomized, placebo-controlled, crossover trial, Park et al. (2018) reported no significant antidepressant effects of scopolamine in treating MDD. Results from animal experiments suggest that increases in glutamatergic transmission, activation of mTOR signaling pathways, and synaptogenesis are associated with scopolamine as well as ketamine (Voleti et al., 2013). Moreover, ketamine and scopolamine have both been shown to provoke transient changes in glutamate cycling in the mPFCs of rats (Chowdhury et al., 2017).

Drugs like psilocybin, LSD, and dimethyltryptamine that act on serotonergic receptors, especially the $5HT_{2A}$-receptor, have been investigated as potential psychiatric treatments in the past (Dos Santos et al., 2016). While many of these studies are indicative of beneficial effects, most of the studies are limited by size and protocol. In a more recent small open-label feasibility study of psilocybin for treatment-resistant depression, a rapid improvement of depressive symptoms was reported (Carhart-Harris et al., 2016). In this trial, the symptoms of depression were reduced for up to three months or more in some patients. Due to major limitations of the study, such as the low number of participants and trial design, no thorough conclusions can be made about the therapeutic efficacy of psilocybin in treating MDD. However, psilocybin has also been investigated in a double-blind placebo-controlled crossover trial in treating patients struggling with severe cancer and related psychological stress (Ross et al., 2016). This study reported rapid and robust anxiolytic and antidepressant effects that endured for at least seven weeks. Upcoming clinical trials will likely unravel the potential that psychedelics may hold as rapid-acting antidepressants.

The most researched non-pharmacological treatment of depression is sleep deprivation. This old experimental practice holds the potential to provide rapid and notable amelioration of depressive symptoms (Boland et al., 2015). In sleep deprivation, patients are kept awake for prolonged periods of time, which results in reduced depressive symptoms for some patients. The effects of sleep deprivation are often short-lived and modest in size, with symptoms returning within days. There is no clear knowledge of the mechanism of how sleep deprivation elicits its effects (Wu & Bunney, 1990). After sleep deprivation, patients exhibit increased rebound slow wave sleep in subsequent sleep periods (Berger & Oswald, 1962; Nakazawa et al., 1978). Moreover, sleep deprivation causes prominent changes in the expression of c-Fos in the rat brain, indicative of cortical activation among other areas (Cirelli et al., 1995). Findings from functional imaging suggest increases in the connectivity of the dorsal nexus to the prefrontal cortex occur in humans after sleep deprivation (Bosch et al., 2013). Moreover, high pretreatment rates of metabolism and subsequent decreases in metabolic rates of the medial prefrontal cortex have been proposed to characterize patients whose depressive symptoms improve after sleep deprivation (Wu et al., 1999; Wu et al., 2008).

Since the discovery of the rapid-acting antidepressant effects of ketamine, clinical research has been carried out with a variety of different drugs, but to date, none of them have produced effects comparable to those of ketamine – that is, rapid and robust antidepressant efficacy in treatment-resistant MDD that is sustained from days to weeks (Henter et al., 2018). Among the drugs that have been investigated for their rapid-antidepressant effects is memantine, an uncompetitive NMDAR antagonist at the PCP-binding site like ketamine. Notably, memantine has failed to produce antidepressant effects in double-blind placebo controlled clinical trials (Lenze et al., 2012; Zarate, Singh, Quiroz, et al., 2006). Relatively rapid antidepressant effects were observed in one study, but this was an open-label trial utilizing dose titration (Ferguson & Shingleton, 2007). These results may be explained by the pharmacodynamic properties of memantine, which is a low-affinity voltage-dependent antagonist with a half-life of 60-100 hours in humans (Matsunaga et al., 2018). It has a unique binding affinity, receptor kinetics, strong voltage dependency, and preference for receptor subtypes and thus brain areas (Parsons et al., 1995; Porter & Greenamyre, 1995). Unlike ketamine, memantine only exhibits partial trapping of the NMDAR ion channels (Blanpied et al., 1997) and has differential effects on receptor desensitization (Glasgow et al., 2017). All the aforementioned properties essentially make memantine a very different type of NMDAR antagonist compared to ketamine. Notably, one of the proposed mechanisms of action for the use of memantine in the treatment of neurodegenerative diseases is its

neuroprotective properties against glutamatergic excitotoxicity (Parsons et al., 1999), while the antidepressant effects of subanesthetic ketamine have been linked to acutely increased glutamate bursting (Moghaddam et al., 1997). Recreational users have reported that memantine can produce potent dissociative effects (Erowid, 2018), but only at doses much higher than those investigated in clinical trials.

Investigational drugs in development include but are not limited to, NMDAR glycine site antagonists, NR2B antagonists, NMDAR glycine site partial agonists, $mGluR_{2/3}$ antagonists, and $mGluR_5$ negative allosteric modulators (Henter et al., 2018). NMDAR antagonists such as MK-0657 (aka CERC-301) (Ibrahim et al., 2012) and AZD6765 (aka lanicemine) (Sanacora et al., 2017), $mGluR_{2/3}$ antagonist RO4995819 (ClinicalTrials.gov, 2018b), $mGluR_5$ antagonist AZD2066 (ClinicalTrials.gov, 2018a), and $mGluR_5$ negative allosteric modulator RO4917523 (basimglurant) (Quiroz et al., 2016) have produced disappointing results in clinical trials, despite having displayed potential effectiveness in animal studies. The difficulty in translating preclinical findings into clinically effective rapid-acting antidepressants thus remains a major issue and may require further understanding of the molecular mechanisms of rapid-acting treatments and the formulation of animal models that are more representative of the key mechanisms mediating rapid antidepressant responses.

3 AIMS OF THE STUDY

There is huge unmet medical need for safer, more efficient, and reliable rapid-acting antidepressants. In addition to ketamine, several other anesthetics like isoflurane (deep anesthesia) and nitrous oxide (subanesthetic) have been shown to provide rapid therapeutic effects in depressed patients. Moreover, the amelioration of depression has occasionally been observed following a single ECT, a phenomenon thought to be linked with postictal EEG slowing. The purpose of this thesis is to utilize such diverse treatments carrying rapid antidepressant potential to find shared neurobiological principles underlying an immediate remedy against major depression.

The specific aims of the study are as follows:

I investigating phosphoproteomic alterations induced by burst-suppressing isoflurane anesthesia,

II investigating the effects of diverse rapid-acting antidepressants on EEG and molecular signatures implicated in ketamine's antidepressant effects and

III investigating the dose-dependent effects of ketamine on TrkB and GSK3β signaling.

4 MATERIALS AND METHODS

The main methods and contributions by the author of this thesis are listed in **TABLE 1**. More detailed information on these procedures can be found in the original publications.

TABLE 1. Methods and author (S.K.) contributions

Method	Used in	Author personally involved
Experimental design	I, II, III	II, III
Pharmacological treatments	I, II, III	I, II, III
Brain dissection	I, II, III	I, II, III
Tissue processing	I, II, III	I, II, III
qPCR	II	II
EEG surgery	I, II, III	II
EEG recordings	I, II, III	II
EEG analysis	I, II, III	
Behavioral experiments	II	
Phosphoprotein enrichment	I	I
LC-MS analysis	I	
Bioinformatics	I	
Writing of manuscript	I, II, III	I, II, III
Statistics	I, II, III	I, II, III
Figures	I, II, III	I, II, III

5 RESULTS

5.1 Phosphoproteomic investigation of the effects of brief isoflurane anesthesia (I)

Previous clinical studies have indicated that isoflurane anesthesia is capable of producing rapid antidepressant effects comparable to those of ECT, without the pronounced cognitive side-effects (Langer et al., 1985, 1995). However, the mechanisms of action of isoflurane anesthesia remain unknown. Moreover, very little is known about the subcellular events following general anesthesia. In general, pharmacological agents can be expected to have a myriad of effects on protein phosphorylation pathways, yet only a few selected targets can be investigated using antibody-based detection of western blots. Thus, we utilized liquid chromatography tandem mass spectrometry (LC-MS/MS) based analysis coupled with titanium dioxide phosphopeptide enrichment to investigate the molecular alterations set forth by a brief isoflurane anesthesia without *a priori* assumptions. To our knowledge, this is the first phosphoproteomic study concerning the effects of anesthesia in samples obtained from the mammalian brain.

We first validated the stable expression of an EEG burst suppression pattern in mice using 4% isoflurane anesthesia for induction and 2% isoflurane for maintenance during a 30 min period. This protocol of isoflurane anesthesia is also commonly used in animal experiments requiring surgical anesthesia. Similar treatment protocol was then used to anesthetize the mice from which the brain samples were collected. We found altogether 318 significant phosphorylation alterations in a total of 237 proteins between the isoflurane anesthetized and sham treated mice. A number of phosphorylation hits represented the primary pharmacological targets of anesthetics, such as the phosphorylation of GABAA α1-subunit Ser373 and Thr366, GABAB β3-subunit Ser394, and NMDAR NR2B subunit Ser1036 and Tyr1039 residues. In addition, several other proteins implicated in a variety of biological processes were identified, including members of solute carriers, ion channels, kinases, and phosphatases. Among these changes, robust regulation of GSK3β at the inhibitory Ser9 residue was identified – a molecular change previously implicated in the rapid-antidepressant actions of ketamine. Moreover, reduced phosphorylation of the activating loop residues of p44/42-MAPK$^{T202/Y204}$ and increased phosphorylation of microtubule-associated protein 2 (MAP2) residues Thr1620,1623 were found. Intriguingly, both of these proteins have been also implicated in mechanisms of antidepressants and plasticity (Bianchi & Baulieu, 2012; Li & Jope, 2010).

The results of the phosphoproteomic analysis were validated using western blotting and commercially available antibodies for GSK3β^{S9}, p44/42-MAPK$^{T202/Y204}$, and MAP2$^{T1620/1623}$. In further experiments, we demonstrated that these three protein targets were all similarly regulated by sevoflurane, urethane, and ketamine – suggesting that these intracellular events are common to all the anesthetics investigated regardless of their somewhat different pharmacological targets (**FIGURE 5**).

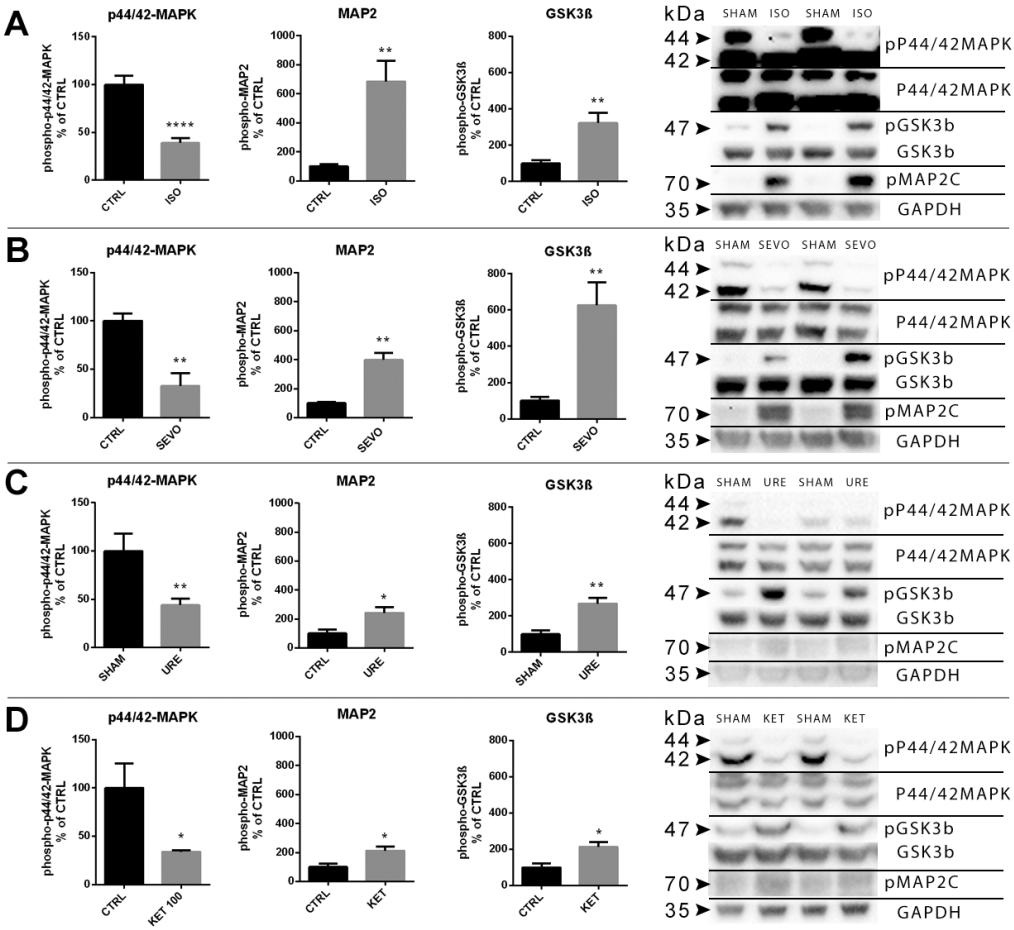

FIGURE 5. Diverse anesthetics produce similar acute phosphorylation changes on p44/42-MAPK$^{T202/Y204}$, GSK3β^{S9}, and MAP2$^{T1620/1623}$ in the adult mouse hippocampus. (A) Effects of isoflurane anesthesia (4% induction, 2% maintenance; 30 min) (N = 10/group). (B) Effects of sevoflurane anesthesia (6% induction, 4.5% maintenance; 30 min) (N = 6/group). (C) Effects of urethane anesthesia (2.0 g/kg, IP; 30 min) (N = 4/control group, N = 6/urethane group). (D) Effects of subanesthetic ketamine (100 mg/kg, IP.; 30 min) (N = 6/group). *p < 0.05, **p < 0.01, ****p < 0.0001; two-tailed unpaired t test with Welch's correction.

Our results provide a foundation for the use of quantitative phosphoproteomics in investigating the neurobiological mechanisms of anesthetic drugs and raise important questions about the functional significance of these phosphorylation changes. Most importantly, these results suggest that isoflurane, sevoflurane, urethane, and ketamine all regulate the phosphorylation changes of GSK3β^{S9}, p44/42-MAPK$^{T202/Y204}$, and MAP2$^{T1620/1623}$ in a similar manner. Furthermore, our results demonstrate that a brief isoflurane anesthesia regulates a myriad of molecular changes that may be confounding factors in many experimental models investigating alterations in cellular signaling.

5.2 Shared neurobiological mechanisms of ketamine, nitrous oxide, and flurothyl (II)

Among the shared properties of the clinically effective rapid-acting treatments ECT and ketamine is the capacity of these treatments to regulate cortical excitability and to modulate several molecular pathways implicated in neuronal plasticity. With the intriguing clinical report of nitrous oxide produced rapid-acting antidepressant effects by Nagele et al. (2015) in mind, we sought to investigate the acute effects of nitrous oxide on EEG parameters and molecular alterations in mice.

We first adopted the treatment protocol used by Nagele et al. (2015) and investigated markers of neuronal excitability using quantitative PCR and western blotting. Mice received 50% N_2O mixed with 50% oxygen for an hour, and the samples were collected one hour after the cessation of the treatment. Samples from the medial prefrontal cortex demonstrated the increased expression of several immediate-early genes: *c-fos, Arc, Bdnf, Zif-268, Homer1A, Egr-2, Mkp-1* and *Synapsin I* (**FIGURE 6A**). Similar changes were also observed in experiments with continued N_2O administration for a duration of two hours after which samples were collected (**FIGURE 6B**). Phosphorylation of p44/42-MAPK$^{T202/Y204}$ was also found to be increased after a 30 min N_2O treatment along with the upregulated expression of *c-fos* mRNA (**FIGURE 6C**). These results suggest increased excitatory tone in the prefrontal cortex under the effects of N_2O. Importantly, these changes bear resemblance to those reported after ECS (Dyrvig et al., 2014) and sleep deprivation (Cirelli et al., 1995).

The administration of subanesthetic ketamine produced an acute increase in gamma EEG oscillations, a marker of neuronal activity, followed by increased slow EEG oscillations after ketamine's elimination (**FIGURE 7A**). These properties prompted us to investigate the EEG alterations arising after the cessation of N_2O treatment. No clear EEG alterations were observed during exposure to 50% N_2O, but upon gas withdrawal, slow EEG oscillations

increased above baseline values (**FIGURE 7B**). We further tested a higher dose of 75% N_2O in a shorter 20-minute exposure to investigate this rebound emergence of slow oscillations and found a rapid increase in delta-frequency power after the cessation of 75% N_2O, which could be repeated by intermittent dosing (**FIGURE 7C**).

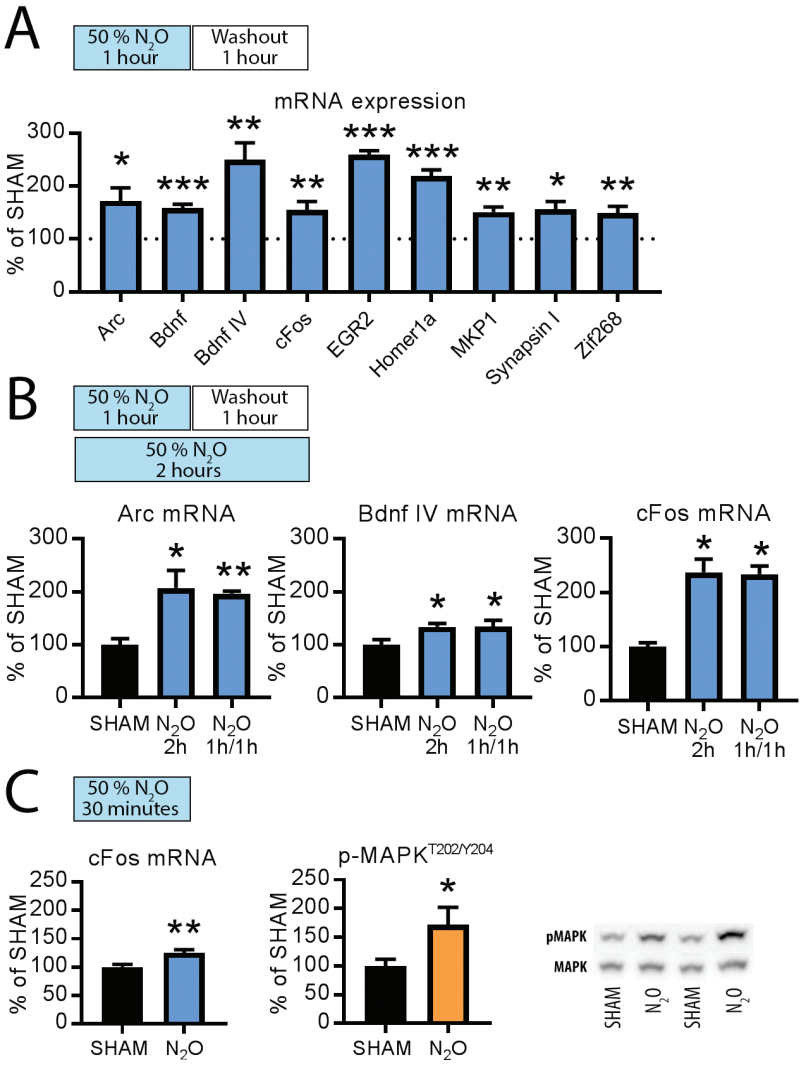

FIGURE 6. (A) Levels of *Arc, Bdnf, c-fos, Egr-2, Homer-1a, Mkp-1, Synapsin 1*, and *Zif-268* mRNA after continuous administration of N_2O (50%) for 1-h and a 1h washout period. (B) *Arc*, *Bdnf*, and *c-fos* mRNA levels are similarly upregulated by 2-h continuous N_2O (50%) and 1-h N_2O (50%) followed by a 1-h washout period. (C) *c-fos* mRNA and p-MAPK$^{T202/Y204}$ levels are increased after 30 min of N_2O (50%) administration. Data are means ± S.E.M. *< 0.05, **< 0.01, ***< 0.001

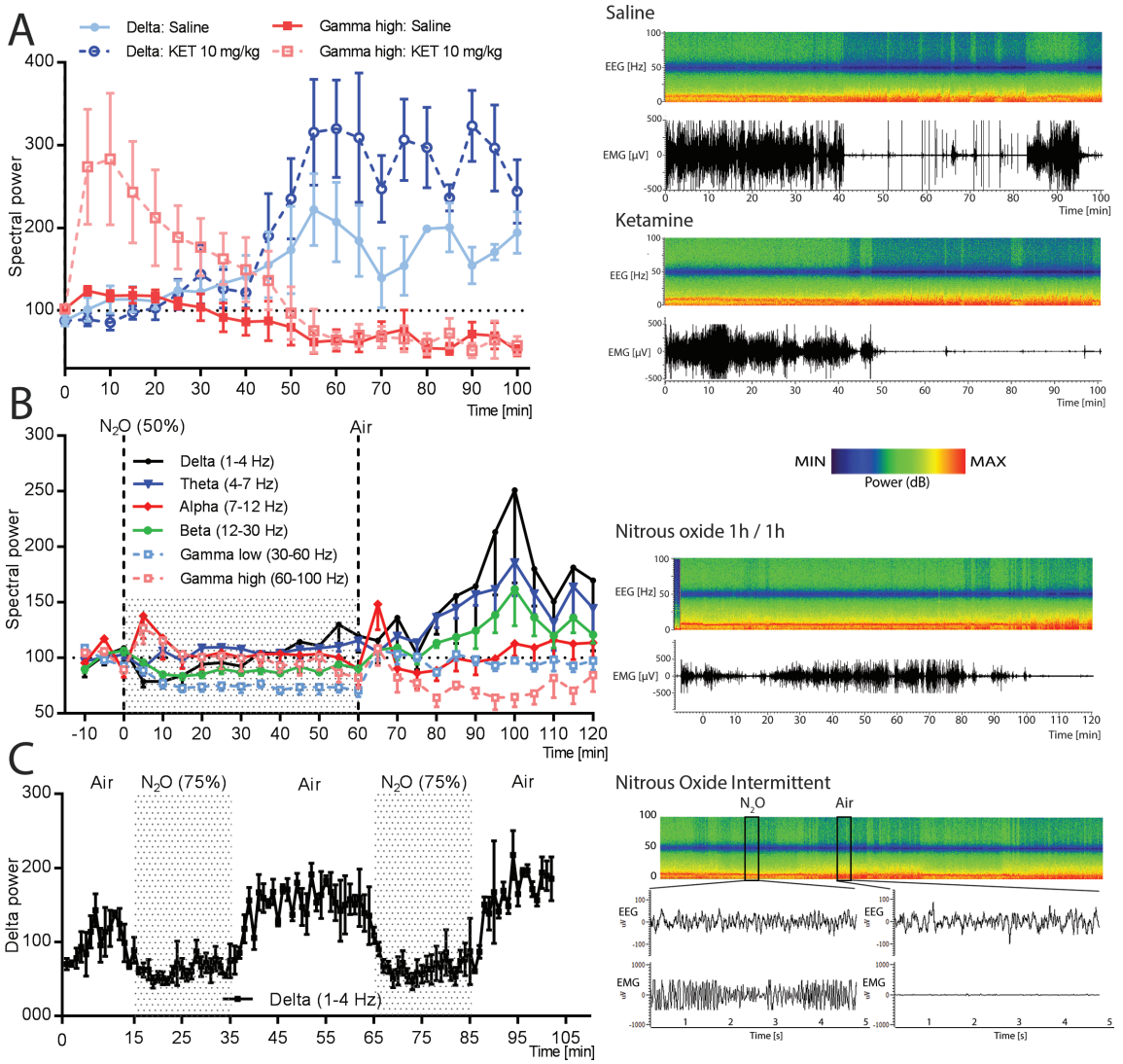

FIGURE 7. (A) Representative time frequency EEG spectrogram and normalized power of EEG oscillations after a subanesthetic dose of ketamine (KET; 10 mg/kg, IP) Subanesthetic ketamine evokes rebound delta oscillations gradually after the acute effects of the drug on high gamma oscillations have dissipated. (B) Slow wave delta (1–4 Hz) and theta (4–7 Hz) EEG oscillations are transiently increased upon N_2O (50%) withdrawal. (C) Rebound delta oscillations after discontinuation of 75% N_2O treatment. Data are means ± S.E.M.

The activation of TrkB, inhibition of GSK3β, and regulation of mTOR signaling have been implicated in antidepressant-like behavioral effects in rodents (Beurel et al., 2011; Li et al., 2010; Saarelainen et al., 2003). We investigated how these molecular pathways are regulated during acute nitrous oxide exposure and during the subsequent withdrawal period. Samples from animals exposed to N_2O for a 30 min period did not show any regulation of the aforementioned pathways (**FIGURE 8A**). However, samples collected during the withdrawal period, 5 or 15 minutes after exposure to N_2O, demonstrated statistically significant phosphorylation changes (**FIGURE 8B-C**). In particular, 65% N_2O was found to produce increased phosphorylation of $TrkB^{Y816}$, $GSK3\beta^{S9}$, and $p70S6K^{T421/S424}$ (a downstream effector of mTOR) after both 5 and 15 minutes during a period of increased slow EEG oscillations (**FIGURE 8B-C**).

The emergence of post-ictal slow EEG activity is also observed in patients following seizures induced with ECT or flurothyl, and this phenomenon has been proposed to predict both the efficacy and onset of the antidepressant effects of convulsive therapies (Fink & Kahn, 1957; Folkerts, 1996; Nobler et al., 1993; Perera et al., 2004; Sackeim et al., 1996; Suppes et al., 1996). We administered flurothyl to mice in amounts that produced a generalized seizure that was terminated rapidly upon drug withdrawal. During the post-ictal period, a robust increase in delta power emerged while the animals appeared motionless and sedated, as evidenced by reduced electromyogram activity (**FIGURE 9A**). When samples were collected during this post-ictal period, the robust regulation of $TrkB^{Y816}$, $GSK3\beta^{S9}$, and $p70S6K^{T421/S424}$ was evident (**FIGURE 9B**). These data suggest that putative rapid-acting antidepressants evoke $TrkB^{Y816}$, $GSK3\beta^{S9}$, and $p70S6K^{T421/S424}$ alterations as during homeostatically generated slow EEG oscillations in response to the preceding period of cortical excitation.

To test whether the direct facilitation of slow EEG oscillations without preceding excitation can also produce these effects, we used medetomidine, a hypnotic-sedative drug commonly used in veterinary anesthesia. Medetomidine increased slow EEG oscillations, but did not produce any acute changes in the expression of IEGs (**FIGURE 10A,C**). Most intriguingly, a sedative dose of medetomidine robustly activated $TrkB^{Y816}$, $GSK3\beta^{S9}$, and $p70S6K^{T421/S424}$ (**FIGURE 10B**), suggesting direct facilitation of slow EEG oscillations to be sufficient for the activation of these pathways.

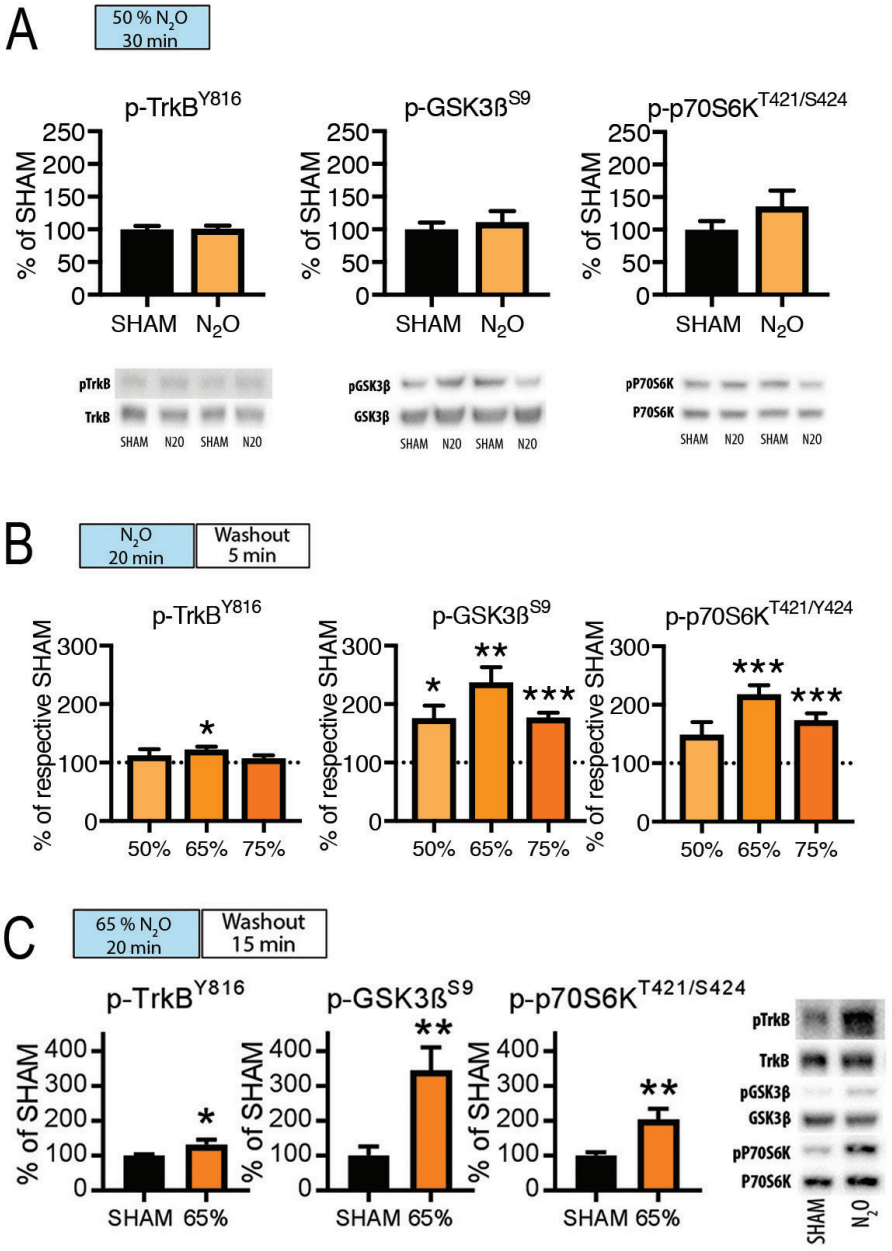

FIGURE 8. (A) Levels of p-TrkB^{Y816}, p-GSK3β^{S9}, and p-p70S6k$^{T421/424}$ after 30 min of N_2O (50%) administration. (B) Levels of p-TrkB^{Y816}, p-GSK3β^{S9}, and pp70S6k$^{T421/424}$ at 5-min post-N_2O exposure (50–75%). (C) Levels of p-TrkB^{Y816}, p-GSK3β^{S9}, and p-p70S6k$^{T421/424}$ at 15-min post-N_2O exposure (65%). Data are means ± S.E.M. *< 0.05, **< 0.01, ***< 0.001.

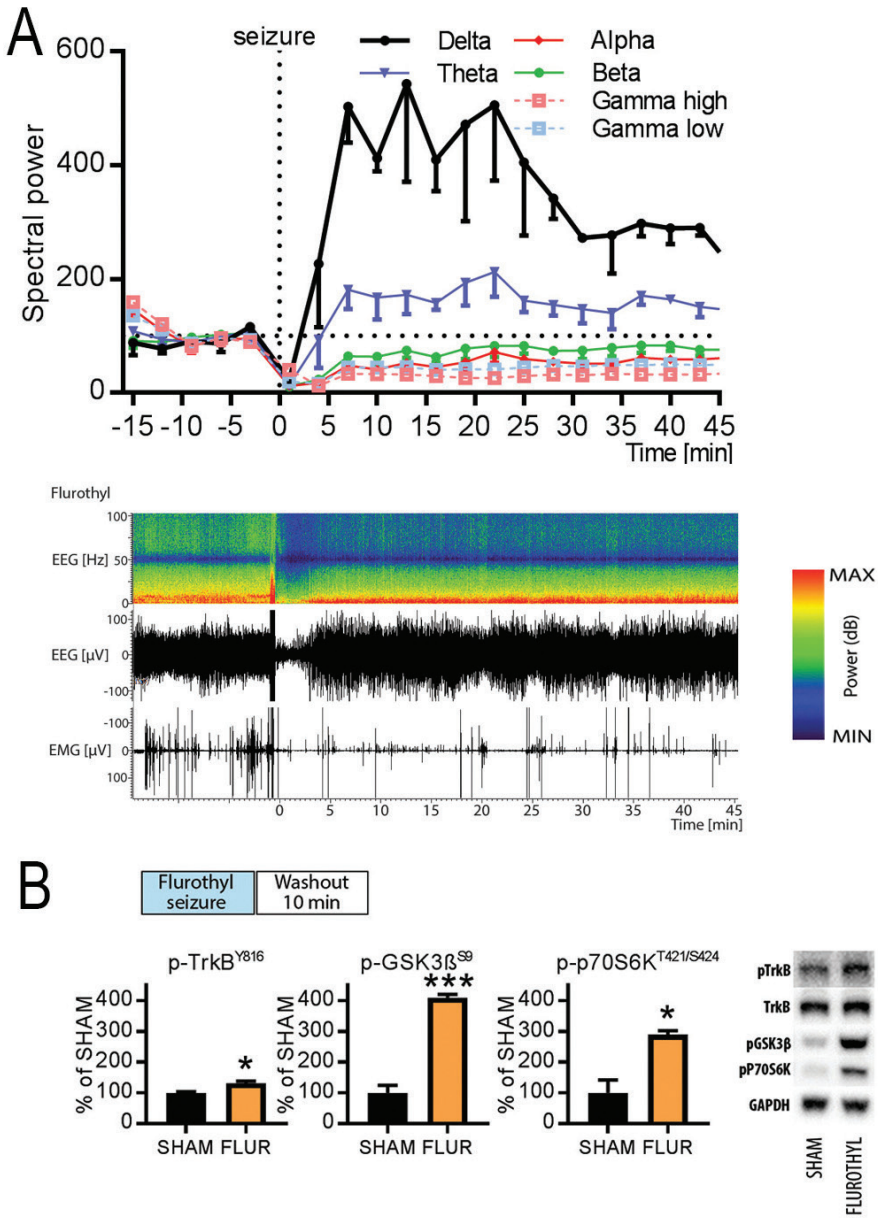

FIGURE 9. (A) Representative time frequency EEG spectrogram and normalized power of major EEG oscillations after flurothyl induced seizures. Flurothyl evokes rebound emergence of slow-wave delta and theta oscillations. (B) Levels of p-TrkB^{Y816}, p-GSK3β^{S9}, and pp70S6k$^{T421/424}$ 10 min after flurothyl (FLUR) administration. Data are means ± S.E.M. *< 0.05, ***< 0.001

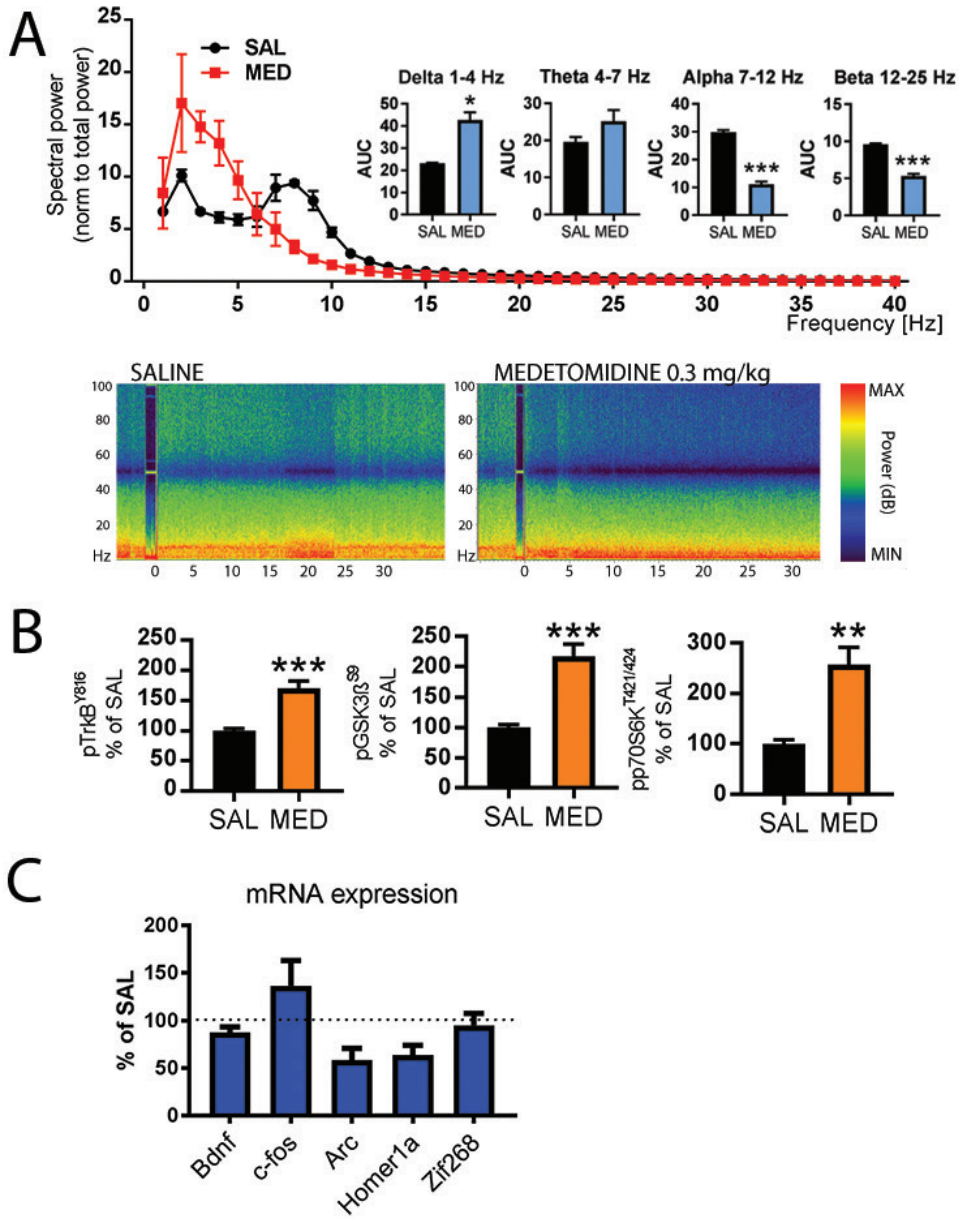

FIGURE 10. (A) Representative time frequency EEG spectrograms and normalized power of major EEG oscillations during 30-min saline and medetomidine (MED; 0.3 mg/kg, IP) treatment. (B) A low dose of medetomidine (0.05 mg/kg, IP) rapidly increases phosphorylation of $TrkB^{Y816}$, $GSK3\beta^{S9}$, and $p70S6k^{T421/424}$ in the mouse medial prefrontal cortex. (C) Levels of *Bdnf, c-fos, Arc, Homer1a* and *Zif268* mRNA 2 h after medetomidine (0.3 mg/kg, IP) administration. Data are means ± S.E.M. *< 0.05, **< 0.01, ***< 0.001

We found that medetomidine, unlike subanesthetic doses of ketamine, reduced the phosphorylation of p44/42-MAPK (**FIGURE 11A**). Since increased phosphorylation of TrkB-mTOR, GSK3β, and MAPK have been thought to be important for ketamine's antidepressant-like behavioral effects, we tested whether medetomidine would produce antidepressant-like behavioral responses without increasing MAPK phosphorylation or regulating immediate-early gene expression. We tested both medetomidine (0.05 mg/kg, IP) and ketamine (15 mg/kg, IP) in the learned helplessness paradigm and found a single dose of subanesthetic ketamine to ameliorate the avoidance deficit, while medetomidine produced no such effect (**FIGURE 11B**)

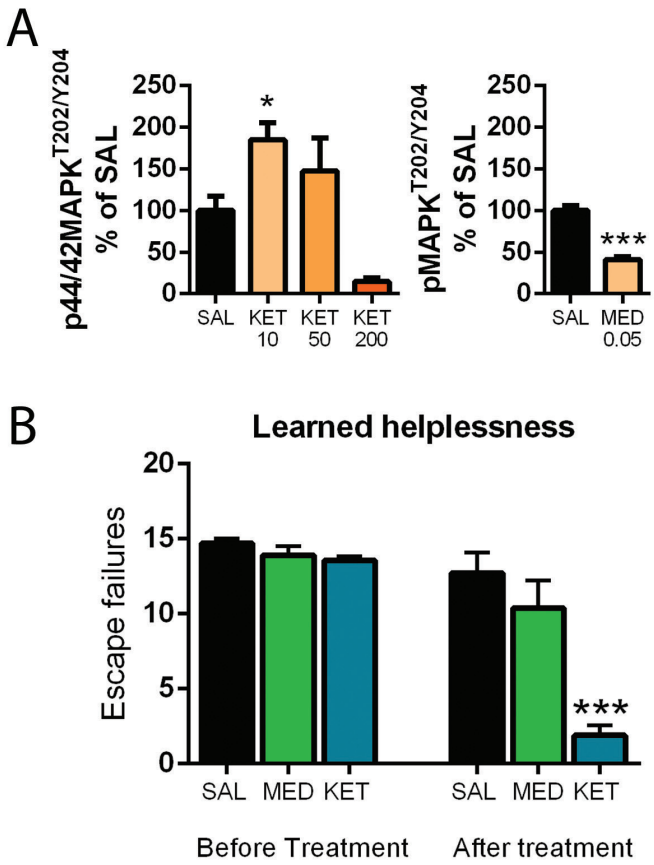

FIGURE 11. (A) Dose-dependent acute effects (30 min) of ketamine (KET) and effects of a low dose of medetomidine (MED; 0.05 mg/kg, IP) on phospho-MAPK$^{T202/Y204}$. (B) Number of escape failures before and 24-h after low-dose ketamine (15 mg/kg, IP) or medetomidine (0.05 mg/kg, IP) in the learned helplessness paradigm. Data are means ± S.E.M. *< 0.05, ***< 0.001

5.3 The regulation of TrkB-GSK3B signaling by ketamine is dose-dependent (III)

Ketamine is most commonly given in subanesthetic doses (~0,5 mg/kg, IV over 40 min) for the treatment of depression. However, a number of studies have suggested that there is a positive relationship between the antidepressant response and the dissociative symptoms produced by the higher-end of subanesthetic doses (Lai et al., 2014; Loo et al., 2016; Luckenbaugh et al., 2014; Niciu et al., 2018; Sos et al., 2013; Xu et al., 2016). Moreover, a recent animal study has suggested that a particular metabolite of ketamine, 6-hydroxynorketamine (HNK), is responsible for ketamine's rapid antidepressant effects (Zanos et al., 2016). Thus, we sought to investigate how different doses of ketamine modulate TrkB-GSK3β signaling and whether these effects rely on ketamine or its metabolites.

Essentially, we investigated the acute effects of ketamine, 6,6-d_2-ketamine (a deuterated ketamine analogue resistant to metabolism), and *cis*-HNK on TrkB and GSK3β signaling and concomitant electroencephalographic (EEG) alterations in the prefrontal cortex of adult mice. A low dose of ketamine (10 mg/kg, IP) increased gamma high power (60-100 Hz), while a higher dose of ketamine (100 mg/kg, IP) prominently facilitated the increase of delta-frequency (1-4 Hz) power along with increases in theta (4-7 Hz), beta (12-25 Hz), gamma low (25-40 Hz) and gamma high (60-100 Hz) power, while decreasing alpha frequency power (7-12 Hz) (**FIGURE 12A-B**). Furthermore, prominent increases in $TrkB^{Y816}$, $p70S6k^{T421/S424}$, and $GSK3\beta^{S9}$ phosphorylation were evident 30 minutes after a higher dose of ketamine, while a low dose failed to produce any changes (**FIGURE 12C**). Most importantly, the ability of ketamine to produce these effects was dose-dependent, with the most significant changes seen after an anesthetic dose.

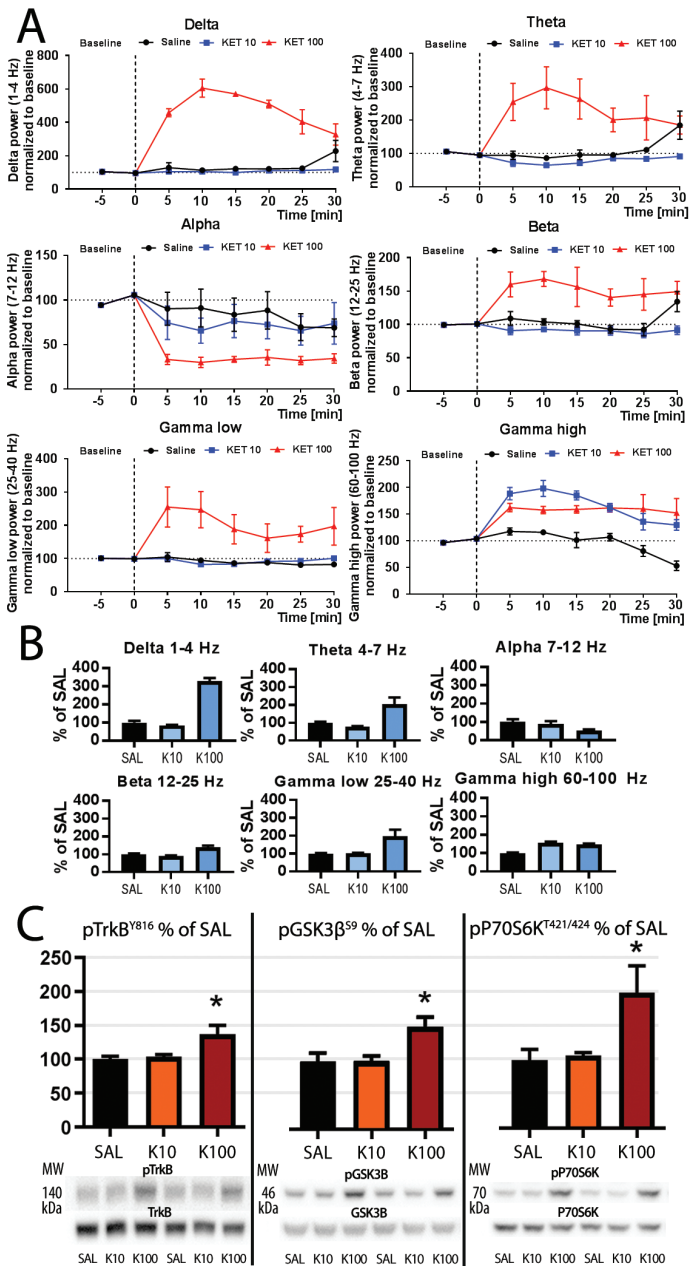

FIGURE 12. (A) Normalized power of major EEG oscillations during ketamine (10 and 100 mg/kg) (data analyzed in 5 min bins). Dashed vertical line indicates injection point (0 min). (B) Major EEG oscillation frequency band power of ketamine treatments represented as area under curve (AUC) from 30 minutes of recording. (C) Phosphorylation of TrkB^{Y816}, GSK3β^{S9}, and p70S6k$^{T421/424}$ in the adult mouse medial prefrontal cortex 30 min after an IP injection of saline (SAL) and ketamine (K10, 10 mg/kg; K100, 100 mg/kg). Approximate molecular weight (MW) for each protein band of interest is given in kilodaltons (kDa). Data are means ± S.E.M. *<0.05, **<0.01, ***<0.005

To elucidate whether these effects are driven by ketamine or by its metabolite HNK, we investigated EEG changes after the acute administration of a high dose of *cis*-HNK (20 mg/kg, IP). *cis*-Hydroxynorketamine produced negligible changes on EEG power spectra when compared to saline-treated animals (**FIGURE 13B-C**). Moreover, tissue samples collected 30 minutes after a similar HNK injection failed to demonstrate any changes in TrkB^{Y816}, p70S6k$^{T421/S424}$, and GSK3β^{S9} phosphorylation (**FIGURE 13A**).

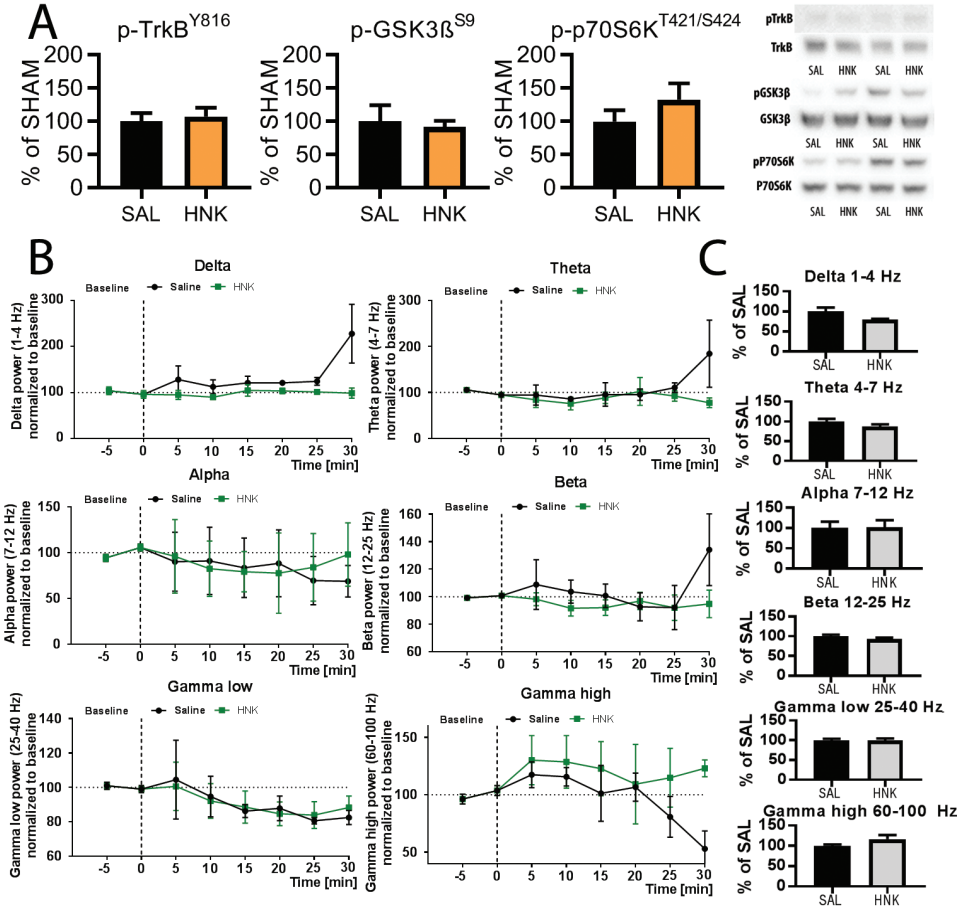

FIGURE 13. (A) Phosphorylation of TrkB^{Y816}, GSK3β^{S9} and p70S6k$^{T421/424}$ in the adult mouse medial prefrontal cortex 30 min after an IP injection of saline (SAL) and *cis*-6-hydroxynorketamine (HNK, 20 mg/kg). (B) Normalized power of major EEG oscillations during HNK (20 mg/kg) (data analyzed in 5 min bins). Dashed vertical line indicates injection point (0 min). (C) Major EEG oscillation frequency band power of HNK treatment represented as area under curve (AUC) from 30 minutes of recording. Data are means ± S.E.M. *<0.05, **<0.01, ***<0.005

The possible role of HNK in mediating signaling effects in conjunction with the parent drug was further tested by rapid sample collection after a very high dose of ketamine and by utilizing a deuterated ketamine analogue resistant to metabolism. A very high dose of ketamine (200 mg/kg, IP) produced rapid phosphorylation changes in PFC samples collected 3 minutes after the injection (**FIGURE 14A**), when the mice appeared to be sedated.

Furthermore, mice were administered equal high doses of either 6,6-d_2-ketamine or ketamine (100 mg/kg, IP). We found that 6,6-d_2-ketamine produced essentially similar effects on TrkB and GSK3β phosphorylation as an equal dose of ketamine (**FIGURE 14B**). These findings reveal that the effects of ketamine on TrkB-GSK3β signaling are by no means restricted to subanesthetic doses and that *cis*-HNK is not solely responsible for these effects.

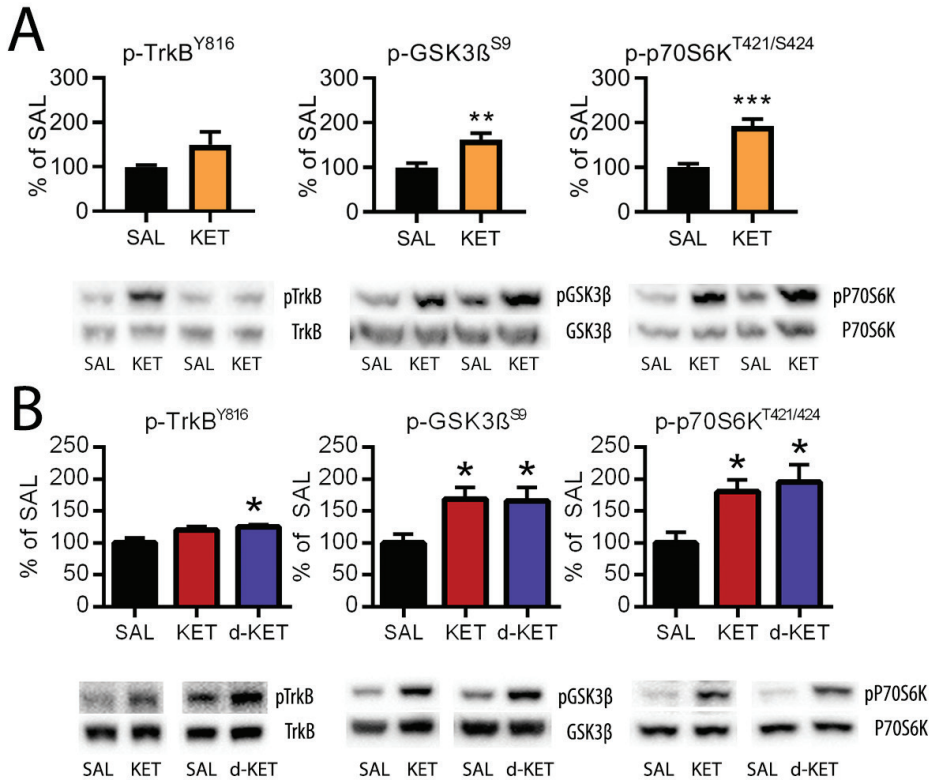

FIGURE 14. (A) Ketamine produces increases in TrkB^{Y816}, GSK3β^{S9}, and p70S6k$^{T421/424}$ in the adult mouse medial prefrontal cortex 3 minutes after an IP injection of saline (SAL) or ketamine (KET, 200 mg/kg). (B) Effects of KET (100 mg/kg, IP; 30 min) and 6,6-dideuteroketamine (d-KET, 100 mg/kg, IP; 30 min) on p-TrkB^{Y816}, p-GSK3β^{S9}, and p-p70S6k$^{T421/424}$. Data are means ± S.E.M. *<0.05, **<0.01, ***<0.005

6 DISCUSSION

6.1 Anesthesia induced phosphoproteomic changes

It has been over 80 years since electroconvulsive therapy was first used to treat psychiatric patients (Cerletti & Bini, 2018). Later, ECT was also found to be effective for treating severe depression (Kalinowsky, 1986). One of the clinically important markers of ECT's action is the post-ictal and/or inter-ictal increase in slow EEG oscillations (Fink & Kahn, 1957; Perera et al., 2004; Sackeim et al., 1996). This EEG slowing has been suggested to underlie the efficacy and onset of action of ECT (Folkerts, 1996; Nobler et al., 1993; Suppes et al., 1996), while not much is known about the molecular correlates of this particular brain state. Intriguingly, in the 1980s, researchers had already set out to investigate whether increasing slow EEG activity and/or burst-suppression with volatile anesthetics such as isoflurane could mimic the effects of ECT and produce therapeutic effects of their own. Indeed, preliminary results from pilot trials with isoflurane have demonstrated effects similar to ECT, without major cognitive side effects (Engelhardt et al., 1993; Langer et al., 1995, 1985; Weeks et al., 2013). The neurobiological mechanisms activated by isoflurane have, however, remained somewhat uncharted.

We investigated the molecular alterations produced by a brief burst-suppressing isoflurane anesthesia in the mouse hippocampi using TiO_2-phosphopeptide enrichment coupled with phosphoproteomics (I). This method can recognize global phosphorylation alterations from sample tissue without *a priori* knowledge. However, this methodology as such does not allow the analysis of changes in precise subdivisions of anatomical structures, such as hippocampal subfields, which may hold differential relevance for depression. Moreover, it does not provide any information on whether the changes are taking place in neuronal or non-neuronal cells, but rather pools all phosphorylation changes together from the sample. It also does not provide an absolute picture of the phosphorylation changes, since TiO_2-based enrichment is thought to enrich phospho-serine/threonine residues better than phospho-tyrosine. With these limitations in mind, the vast number of changes demonstrated by our study is a solid indicator of the widespread molecular alterations set forth by brief burst-suppressing isoflurane anesthesia. Since similar anesthesia procedures are very commonly used in preclinical research, these findings raise important questions about the confounding effects of anesthesia on phosphoprotein analyses (e.g. immunohistochemistry following transcardiac perfusion) and assays in general. This is especially important since some of phosphorylation changes elicited by isoflurane appear rapidly after brief exposure and may have long

lasting effects on animal behavior (Antila et al., 2017; Brown et al., 2018).

Altogether, 318 phosphorylation alterations were identified in a total of 237 proteins, which are fully represented and discussed thoroughly in the original publication (I). Here I will focus on selected hits, which are also relevant for the other studies. These hits are GSK3β^{S9}, p44/42-MAPK$^{T202/Y204}$, and MAP2$^{T1620/1623}$, which were confirmed using western blotting and site-specific antibodies. Moreover, we investigated whether the same residues were affected by other anesthetics drugs at high doses: ketamine, urethane, and sevoflurane. To our surprise, all the anesthetics had similar effects on the phosphorylation of these selected molecular targets, even though their pharmacological mechanisms are not entirely identical. For example, the volatile anesthetics isoflurane and sevoflurane profoundly increase the activity of inhibitory $GABA_A$ receptors that are already at clinically relevant concentrations, while drugs like ketamine are not known to have similar effects (Krasowski & Harrison, 1999). Furthermore, isoflurane and sevoflurane are known to increase glycine-induced Cl^- currents, while ketamine does not modulate the glycine receptor. On the other hand, ketamine has more potent effects on the inhibition of NMDA receptors (Yamakura & Harris, 2000). Urethane likely has the widest profile of pharmacological targets. It induced increases in glycine and $GABA_A$ receptor function, while its inhibition of NMDA and AMPA receptors is considered more modest (Hara & Harris, 2002). Based on these findings, we hypothesized that these anesthetics may cause some molecular alterations by having similar effects on the global brain state (i.e. anesthesia or sedation) despite the differences in their main pharmacological targets.

Several of the discovered hits are involved in the regulation of the cytoskeleton and microtubule dynamics. Among these, microtubule-associated proteins (MAPs) like MAP2 play a role in coordinating the bundling activity of microtubules that form anchoring scaffolds for other proteins to interact with. MAPs are known to be heavily regulated by phosphorylation, which changes their ability to bind to microtubules and stabilize their structure (Sánchez et al., 2000). MAP2 phosphorylation in Thr1620/1623 residues is known to render its dissociation from microtubules in vitro (Sánchez, Pérez et al., 2000). Thus, there can be various downstream effects of the phosphorylation of MAPs, including changes in the regulation of organelle transport and anchorage of protein kinases and phosphatases. The actions of microtubules and MAPs have been also been proposed to be relevant for psychiatric disorders (Marchisella et al., 2016). Intriguingly, some studies have implicated actions on MAP2 in the putative antidepressant effects of neurosteroid drugs (Bianchi & Baulieu, 2012; Daftary et al., 2017). The association of microtubule-related functions with psychiatric disorders thus remains a promising avenue for fur-

ther research, which may also hold relevance for the antidepressant effects of anesthetic drugs.

Among the phosphorylation alterations induced by the anesthetics, we observed an increase in the phosphorylation of GSK3β Ser9 residue (I), which inactivates (Frame et al., 2001) this promiscuous kinase (Linding et al., 2007). This phosphorylation event has been previously suggested to be necessary for the rapid antidepressant-like effects of ketamine observed in mice (E Beurel et al., 2011). Moreover, we observed a reduction in the p44/42-MAPK phosphorylation of the Thr202/Tyr204 residues with all anesthetics. The MAPK pathway has also been implicated in the behavioral effects produced by antidepressants and ketamine (Duman et al., 2007; Li et al., 2010; Réus et al., 2014). In particular, *in vivo* studies indicate increased phosphorylation of p44/42-MAPK in antidepressant effects, while the blockade of MAPK activity using MEK inhibitors diminishes these effects (Duman et al., 2007; Pochwat et al., 2017).

The phosphorylation of p44/42-MAPK is generally thought to increase in response to excitatory neuronal activity, and it is increased rapidly and robustly after ECS (Baraban et al., 1993; Bhat et al., 1998; Yamagata et al., 2002). Indeed, MAPK phosphorylation is increased in *ex vivo* brain slices by glutamate administration and mediates the phosphorylation of the transcription factor CREB and the expression of cFos (Vanhoutte et al., 1999). Many studies, in the context of rapid-acting antidepressant effects, have investigated the effects of subanesthetic doses of ketamine (~10 mg/kg, IP), while the decreased phosphorylation of MAPK in our study may represent the molecular changes particularly associated with more anesthetic states, since we used a dose of 100 mg/kg. Importantly, Li et al. (2010) reported increased phosphorylation of p44/42-MAPK after 10 mg/kg, but not after 80 mg/kg of ketamine when measured in the PFC of rats one hour after administration. However, they analyzed synaptosomal fractions instead of raw lysates. Nevertheless, the differential regulation of glutamate dynamics with small and large doses of ketamine remains a plausible explanation for the decrease in MAPK phosphorylation after a 100 mg/kg dose of ketamine IP. While 100 mg/kg of ketamine is not sufficient to produce surgical anesthesia, it does produce visible behavioral immobility unlike much lower subanesthetic doses, and in this way corresponds to the anesthetic states produced by isoflurane, sevoflurane, and urethane, which also reduced MAPK phosphorylation (I).

MAPK phosphorylation is increased in vitro in primary cultured neurons by rapid-acting antidepressants and is thought to be dependent on both AMPA and TrkB receptors (Lepack et al., 2016). According to Lepack et al., this increase in MAPK phosphorylation was not evident with traditional antidepressants, which suggests that it might be a particular property of rapid-acting

treatments at least in primary cultures. Other studies have also connected neurotrophic signaling via the BDNF receptor TrkB with the antidepressant-like behavioral effects of both traditional and rapid-acting antidepressants (Saarelainen et al., 2003; Sun et al., 2016). Chronic treatment with traditional antidepressants is known to increase the synthesis of BDNF (Nibuya et al., 1995), which has been proposed to act through its cognate receptor TrkB to promote plasticity (Karpova et al., 2011; Vetencourt et al., 2008). However, antidepressants can also transactivate TrkB in the absence of BDNF (Rantamäki et al., 2011), and similar transactivation may occur with isoflurane, sevoflurane, and halothane (Antila et al., 2017).

One of the downstream targets of neurotrophic signaling is the mTor pathway, a key regulator of protein synthesis and cellular metabolism (Magnuson et al., 2012), which has been proposed to underlie some of the changes in synaptic proteins and spine formation following ketamine administration in rodents (Li et al., 2010). Activators upstream of mTOR are protein kinase B (i.e. Akt) and MAPK (Inoki et al., 2006). Furthermore, the activation of GSK3β inhibits mTor activation. Downstream of mTor is the ribosomal protein S6 kinase beta-1, also known as p70S6K (Magnuson et al., 2012), a serine-threonine kinase that is phosphorylated and activated consequently via mTOR activity by ketamine in the prefrontal cortex of rats (Li et al., 2010). The activation of p70S6K further targets the S6 ribosomal protein, which induces protein synthesis at the ribosome (Magnuson et al., 2012). While this study did not reveal phosphorylation changes on p70S6K, we investigated these in another study and found increased phosphorylation after isoflurane anesthesia in the hippocampus and mPFC of mice (Antila et al., 2017).

6.2 Nitrous oxide regulates neuronal signaling events implicated in rapid antidepressant effects

The intriguing clinical report by Nagele et al. (2015) led us to investigate whether nitrous oxide, a gaseous anesthetic, would produce similar molecular alterations to those previously witnessed after ketamine and isoflurane. We were surprised to find that an acute 30 min nitrous oxide (50% N_2O/O_2) treatment had little impact on the phosphorylation levels of $TrkB^{Y816}$, $p70S6k^{T421/S424}$, and $GSK3\beta^{S9}$ measured from mPFC samples (II). It did, however, increase the phosphorylation of $p44/42\text{-}MAPK^{T202/Y204}$, suggesting increased cortical excitability taking place during N_2O administration. Indeed, nitrous oxide readily regulated the expression of multiple IEGs (*Arc, Bdnf, Bdnf exon IV, cFos, EGR2, Homer1a, MKP1, Synapsin 1*, and *Zif268*). In further support of this idea, a pre-

vious study has suggested that the cerebral metabolic rate (CMR) is increased during nitrous oxide anesthesia in goats (Pelligrino et al., 1984). Increases in cerebral blood flow (CBF) with nitrous oxide inhalation have also been measured in humans (Deutsch & Samra, 1990; Field et al., 1993).

We also conducted EEG measurements during and after nitrous oxide treatment, which revealed that once the gas administration ceased, mice exhibited increased slow EEG oscillations – a phenomenon also reported in human trials (Foster & Liley, 2011; Henrie et al., 1961; Williams et al., 1984). Since we had previously seen phosphorylation changes in $GSK3\beta^{S9}$ and $p44/42\text{-}MAPK^{T202/Y204}$ after high doses of various anesthetics known to silence EEG activity (I), we investigated whether these molecular alterations are present during the increased slow EEG activity following the cessation of nitrous oxide administration. Indeed, nitrous oxide increased TrkB, GSK3β, and p70S6K phosphorylation in mPFC samples collected after the cessation of gas flow (II). Moreover, a subanesthetic dose of ketamine (10 mg/kg, i.p) produced a similar homeostatic rebound of slow EEG oscillations after the acute pharmacological effects of the drug were dissipated. We continued to test the connection between excitatory activity, subsequent EEG slowing, and the associated molecular changes by utilizing flurothyl to trigger generalized seizures. These seizures were followed by prominent post-ictal increases in slow EEG activity, and when mPFC samples were collected during this state, significant increases in the phosphorylation of TrkB, GSK3β, and p70S6K were noted. Phosphorylation of TrkB, GSK3β, and p70S6K, however, remain unaltered immediately following the seizure when slow oscillations had not yet emerged (Rosenholm M, unpublished). Thus, we hypothesized that ketamine, nitrous oxide, and flurothyl drive excitatory activity in the cortex, to which the brain responds with the homeostatic emergence of rebound slow EEG activity. We also hypothesized that during this process, TrkB signaling becomes activated.

Since nitrous oxide produced an upregulation of Bdnf expression (II), the synthesis of BDNF and its actions through TrkB receptors may be involved in the subsequent emergence of slow EEG activity. Interestingly, BDNF injected intracerebroventricularly in rats and rabbits has been shown to produce increases of time spent in non-rapid eye movement (NREM) sleep (Kushikata et al., 1999), and cortical unilateral microinjections of BDNF have been shown to increase SWA in the injected hemisphere during subsequent sleep periods. On the other hand, TrkB receptor inhibitor K252a produces a decrease in SWA (Faraguna et al., 2008). In addition, BDNF has been demonstrated to modulate baseline and homeostatic regulation of REM sleep (Garner et al., 2018). These findings are most interesting since BDNF is also upregulated by ECT, and sleep disturbances are a key feature of depression (Breslau et al., 1996;

Germain et al., 2004). However, since we did not investigate acute changes in BDNF levels in our study or elucidate whether TrkB activation was dependent on BDNF, these ideas remain speculative. The results of these studies and effects of rapid-acting antidepressants on rebound SWA should be investigated in *Bdnf* deficient animals.

BDNF signaling via its cognate receptor TrkB is thought to be dependent on neuronal activity and to control activity-dependent plasticity (Ernfors et al., 1991; Hall et al., 2000; Poo, 2001). However, the receptor may also be transactivated independently of BDNF (Rantamäki et al., 2011). The phosphorylation of TrkB, particularly during sedative states, accompanied by increased slow EEG activity, may thus suggest activity- and BDNF-independent mechanisms. This transactivation of TrkB receptors has been proposed to also occur during isoflurane anesthesia (Antila et al., 2017). In our study, however, we did not further elucidate the molecular mechanisms behind TrkB activation. It has been suggested that BDNF-induced activation of TrkB phosphorylates Y515 residue acting as the Shc binding site (Guo et al., 2014; Segal et al., 1996) could be possibly used to distinguish between BDNF-dependent and independent activation, since this site is not phosphorylated by isoflurane (Antila et al., 2017). A better strategy would be to utilize forebrain-specific *Bdnf* knockout mice and test whether TrkB phosphorylation events take place in these animals in response to the treatments. It also remains to be investigated whether TrkB activation during increased slow EEG oscillations recruits other canonical downstream pathways and if the phosphorylation of p70S6K and GSK3β are dependent on TrkB activation.

These effects of anesthetics may be dependent on direct receptor-mediated mechanisms, but on the other hand, these changes could also occur in response to more global changes in neuronal metabolism and network activity. Notably, many previous studies have reported abnormalities in the regulation of energy metabolism in association with MDD, including deficits in cerebral blood flow (Bench et al., 1993; Schlegel et al., 1989), glucose metabolism (Baxter et al., 1989; Li et al., 2015), and mitochondrial function (Allen et al., 2018). For example, a high resolution positron emission tomography study looking at the effects of ECT on CBF reported an increase during seizure activity in the basal ganglia, brainstem, diencephalon, amygdala, and vermis as well as in the frontal, temporal, and parietal cortices, while a decrease was evident during the post-ictal period in the anterior cingulate and frontal cortex (Takano et al., 2007). Both the anterior cingulate and the frontal cortex have been implicated in the pathophysiology of depression (Drevets, 2000), and the reduction of blood flow to these areas have been associated with positive clinical responses (Nobler et al., 1994). These results of decreased postictal CBF in the cortex are

also in line with the vast literature of EEG studies related to postictal anterior slowing after ECT (Fosse & Read, 2013) and our findings of EEG slowing after flurothyl-induced seizures. However, further studies are needed to fully understand the similarities and differences between the postictal state and the rebound increase of slow EEG oscillations after nitrous oxide and ketamine administration.

6.3 Medetomidine increases TrkB-GSK3β signaling, but does not produce antidepressant-like behavioral effects

We pursued the connection between slow EEG activity and the observed molecular signaling mechanisms further using medetomidine, a sedative drug with a completely different pharmacological mode of action than nitrous oxide and ketamine (II). Unlike NMDA antagonists, medetomidine activates α_2-adrenergic autoreceptors and decreases neurotransmitter release (Sinclair, 2003). We demonstrated that medetomidine produces a rapid increase in slow frequency power after an IP injection in mice – similar to that seen in humans during dexmedetomidine sedation (Sleigh et al., 2018; Xi et al., 2018). Moreover, to validate the claim of medetomidine not producing cortical excitation, we demonstrated that medetomidine does not induce changes in the expression of IEGs in the mPFC two hours after drug administration. Most importantly, when brain samples were collected 30 min after the injection of medetomidine, during the medetomidine-induced slow EEG activity, we saw robust increases in TrkB, GSK3β, and p70S6K phosphorylation, while p44/42-MAPK phosphorylation was downregulated. These results suggest that these molecular alterations are either driven by the brain state characterized by increased slow EEG activity or coincide with it.

We continued to investigate whether the direct facilitation (i.e. not rebound emergence) of slow EEG oscillations and the accompanying phosphorylation alterations (but lack of excitatory markers) induced by medetomidine produces antidepressant-like responses in the learned helplessness (LH) model of depression (II). In our experiments, untreated mice were first exposed to inescapable mild foot shocks during two pre-test days, which effectively rendered the animals helpless – that is, they no longer tried to escape the unpleasant stimuli. On the third day, the animals were tested again with the possibility of escaping the shocks by crossing into another chamber. After this, saline, ketamine or medetomidine was administered, and the animals were retested again 24 hours later to quantify changes in their avoidance behavior. Notably, medetomidine failed

to elicit any antidepressant-like effects in the learned helplessness model, but subanesthetic ketamine effectively ameliorated the avoidance deficit.

Previous studies have demonstrated that both ketamine (Autry et al., 2011; Beurel et al., 2011; Li et al., 2010; Zanos et al., 2016) and ECS (Biedermann et al., 2012; Sartorius et al., 2003) produce antidepressant-like effects in the LH. However, it is important to keep in mind that all behavioral tests in rodents have limitations. Despite the possibility that the behavioral results might not be measuring antidepressant effects as such, these findings provide novel evidence of medetomidine-induced phosphorylation of TrkB, GSK3β, and p70S6K without promoting antidepressant-like behavioral outcomes (II). Besides antidepressant drugs and anesthetics, the acetylcholinesterase inhibitors donepezil and galantamine have also been shown to activate TrkB in the mouse hippocampus, while not affecting MAPK phosphorylation (Autio et al., 2011). Since drugs like medetomidine and donepezil are not known to have antidepressant effects in humans, TrkB activation by itself does not seem to be sufficient for clinically effective therapeutics. It may also be the case that the phosphorylation alterations we see during slow EEG activity are not relevant for treating depression *per se*, but may hold other neurobiological significance, for example in the cascade of events that leads to putative alterations in neuronal network function.

One of the clearest differences between medetomidine and ketamine is their differing ability to affect cortical excitability. Above all, clinical evidence supports the excitatory activity of nitrous oxide and ketamine and the lack of excitatory activity for pharmacological sedatives. For example, nitrous oxide has been reported to increase global CBF via the augmentation of blood flow in frontal cortical areas, but increases have also been noted in the basal ganglia, insula, and thalamic regions (Reinstrup et al., 1994). In a PET imaging study, nitrous oxide on was found to have a minor but not statistically significant effect on global CMR (Reinstrup et al., 2008). However, the inhalation of nitrous oxide was shown to change the regional distribution of CMR, with increases in the thalamus and the basal ganglia. Moreover, nitrous oxide may particularly increase metabolism in the limbic system (Reinstrup et al., 2008, 1994), which is also supported by experiments using depth-electrode measurements of the limbic and thalamic regions in epileptic patients who displayed increased activity after ketamine and nitrous oxide administration (Ferrer-Allado et al., 1973). On the other hand, sedative drugs like midazolam that lack any obvious antidepressant effects seem to reduce regional CBF in regions including the prefrontal cortex and thalamus (Veselis et al., 1997). Furthermore, a clinical study comparing dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional CMR using PET imaging reported that only S-ketamine did not reduce CMR (Laaksonen et al., 2018).

6.4 Two phases of rapid antidepressant action: a hypothesis

Based on our findings, we formulated a hypothesis of the two-phased action of rapid-acting antidepressants in the brain (**FIGURE 15**). According to our hypothesis, the first phase of action takes place during the acute pharmacological effects – that is, during N_2O inhalation or during ongoing ketamine infusion, when the cerebral cortex is directly under the influence of said rapid-acting antidepressant. The acute drug-induced excitation may be reflected by EEG changes, such as increased gamma power during ketamine administration, or measurable as molecular changes (e.g. increased IEG expression and increased phosphorylation of MAPK). The excitatory phase then results in the emergence of homeostatic slow EEG oscillations in the second phase, when the drug has been cleared, metabolized, or excreted from the body. We speculate that this increase in slow EEG activity is an inherent property of neuronal networks responding to the preceding excitation, and during this state, the phosphorylation alterations in neurotrophic pathways (e.g. increases in TrkB, GSK3β, and p70S6K and decreases in p44/42-MAPK phosphorylation) also become activated via endogenous mechanisms. However, the direct induction of these phosphorylation alterations by triggering a sedative brain state or increasing slow wave activity without the preceding excitatory drive may not be enough to achieve therapeutic effects (i.e. medetomidine).

Since our hypothesis suggests cortical excitation and the subsequent regulation of molecular alterations during slow EEG oscillations as the driving forces behind the therapeutic effects of rapid-acting treatments, one must ask how these fit into the putative rapid-acting antidepressant effects of general anesthetics such as isoflurane or propofol. Notably, it has been suggested that general anesthetics do not cause a global suppression of neuronal activity, but result in more differential effects on cortico-cortical and thalamo-cortical networks (Alkire et al., 2008; Liu et al., 2013; Mashour & Alkire, 2013). Moreover, general anesthetics may produce transient excitatory effects both during the induction of anesthesia and during emergence from anesthesia, which are often called "emergence phenomena" (Cascella et al., 2018). These effects appear to take place particularly during periods when the concentration of the drug being administered has not yet reached anesthetic levels or has been reduced from anesthetic concentrations (Kuizenga et al., 1998, 2001). The molecular alterations coinciding with these phases of anesthesia remain to be investigated in this context.

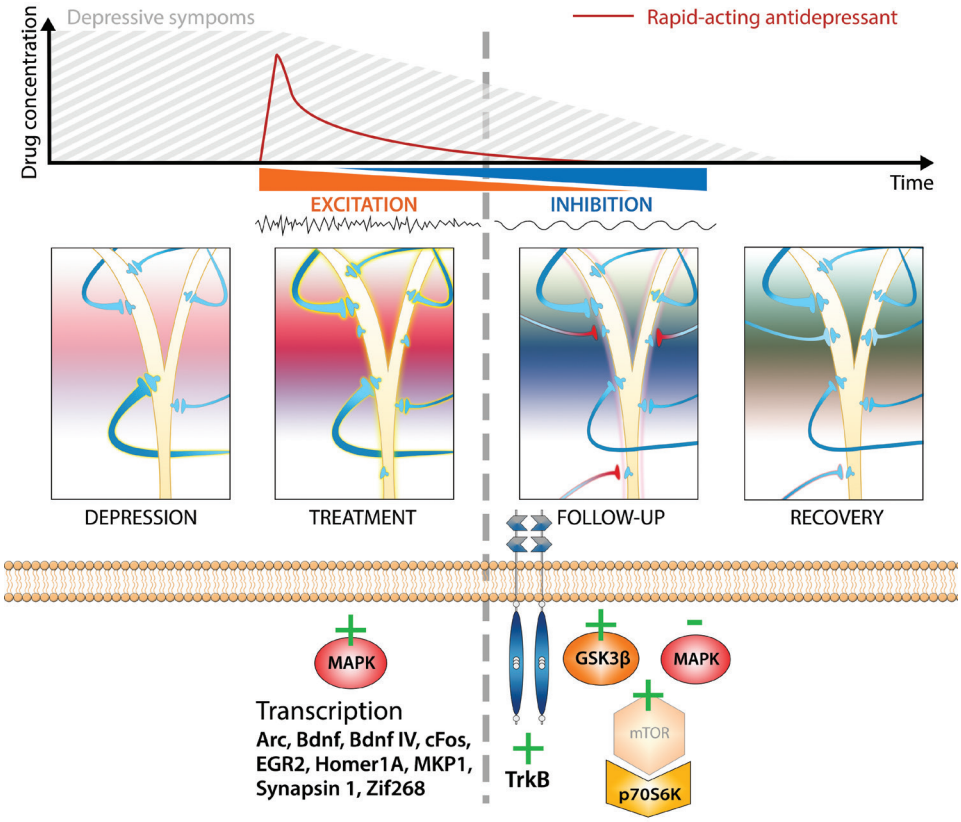

FIGURE 15. Hypothesis of the two phases of rapid-acting antidepressant action. The first phase (left side of the dashed line) occurs during the acute pharmacological challenge and is characterized by increases in cortical excitability and synaptic potentiation. It is also marked by changes in the transcription of immediate-early genes and increased MAPK phosphorylation. The second phase (right side of the dashed line) occurs when the rapid-acting antidepressant is no longer present, and is characterized by an increase in the homeostatic regulation of slow EEG activity coinciding with increased phosphorylation of TrkB, GSK3β, and p70S6K (downstream of mTOR), while MAPK phosphorylation is reduced. These alterations may, for example, coincide with the consolidation of activity-driven changes or initiate synaptic downscaling, ultimately resulting in the reconfiguration of network activity. Increased phosphorylation is marked by (+) and decreased phosphorylation by (-).

Our results bring up a further important aspect to consider, which is related to the pharmacokinetic properties of neuropharmacological drugs. Ketamine, for instance, has a relatively rapid rate of metabolism, which makes the acute pharmacological effects of the drug brief. For example, in the study of Li et al. (2010), ketamine (10 mg/kg, IP) administered to rats produced a rapid increase in the phosphorylation of p44/42-MAPK and Akt in the PFC that was visible both 30 minutes and 1 hour after the injection, but not at sub-

sequent time points. This time course seems to readily follow the half-life of ketamine. Since post-translational modifications like the phosphorylation of proteins can be regulated in a scale of minutes, the precise time point of the collection of samples may have significant influence over the state of phosphorylation events. This is best exemplified by our results regarding N_2O, which is essentially removed from the body almost instantaneously once the gas flow is ceased. In the experiments with N_2O, a brief change in the sample collection time reflected surprisingly different results.

Hypothetically, the rapid clearance of ketamine may also be important for its therapeutic effects, since many other NMDAR antagonists have failed to demonstrate such robust antidepressant effects. Memantine, for example, has a half-life that is between 60 and 100 hours in humans (Matsunaga et al., 2018), and has been given to patients daily in clinical trials studying its antidepressant effects (Lenze et al., 2012; Zarate, Singh, Quiroz, et al., 2006). Besides the differences in the pharmacology of ketamine and memantine, the differences in the pharmacokinetic properties and dosing pattern also differentiate these treatments. According to our hypothesis, the rapid clearance and "pulse-like" administration of ketamine allows the drug to briefly excite the cortex and then give way to the subsequent phases of homeostatic realignment. Contrary to ketamine, once memantine is administered, it acts in the brain for days. If stable concentrations of the drug are reached through chronic daily administration, the homeostatic response of the brain will be to readjust to maintain that state. Indeed, the relatively brief duration of action is a shared property of ketamine, N_2O, isoflurane, propofol, and ECT. Rapid-acting antidepressants are also pharmacologically rapid-acting. Most importantly, the effects of rapid-acting antidepressants seem to become most evident when the drug has already been cleared from the body, suggesting that lasting changes took place during administration. Furthermore, the effects may last from days to weeks after just one single treatment, suggesting that the rapid changes initiated by the drug are consolidated to some degree. These properties share similarities with what is known about the mechanisms of memory, a property of neuronal networks that illustrates similar rapidly induced but long-lasting changes.

Physiologically, a strong stimulus may trigger the formation of memories, recapitulated by changes in synaptic strength via mechanisms such as protein phosphorylation and increases in synaptic function via LTP (Bear, 1997; Nicoll, 2017). Without subsequent consolidation, the synaptic strengths decay back and the encoded information is lost. Short-term memories have been proposed to transform into long-term memories through a process called synaptic tagging (Frey & Morris, 1997). In synaptic tagging, a stim-

ulus establishes molecular "tags" in specific synapses that can then become further potentiated (i.e. L-LTP) by later associating with newly synthesized plasticity-related proteins. In L-LTP, changes in postsynaptic gene transcription are thought to be triggered (Pittenger & Kandel, 1998). Kinases already triggered during E-LTP are thought to contribute to L-LTP, such as MAPK (Thomas & Huganir, 2004), CaMKII (Ma et al., 2014), Akt (Pen et al., 2016), PI3K (Asrar et al., 2009) and PKC subtypes (Jalil et al., 2015), many of which are also putative downstream (or upstream) targets of TrkB signaling. These pathways then further contribute to the phosphorylation of other targets, such as transcription factors like CREB (Barco et al., 2002), which further leads to changes in protein synthesis by key regulators like mTOR (Hay & Sonenberg, 2004; Tang et al., 2002). *De novo* protein synthesis is suggested to be required for the maintenance of induced LTP, which is relevant to the formation of lasting memories (Bekinschtein et al., 2007; Goelet et al., 1986) and to the behavioral effects of ketamine (Girgenti et al., 2017; N. Li et al., 2010).

It is plausible that major differences in the extent, duration, and selectivity of the excitatory activity produced by rapid antidepressant treatments may also determine their functional consequences. While flurothyl (and ECT)-induced seizures are a very pronounced form of global excitatory activity, ketamine and nitrous oxide seem to drive this excitation in a subtler way. It may be that during the excitatory phase, IEGs are produced by the activation of, for example, particular thalamocortical networks, which leads to their translation during the subsequent period of slow EEG activity, and ultimately leading to sustainable functional changes. This way, network activity, for example, in the form of synaptic tagging (Frey & Morris, 1997) or inverse synaptic tagging via mechanisms implicating Arc (Okuno, Akashi, Ishii, Yagishita-Kyo, et al., 2012), may be consolidated in subsequent phases. Moreover, excitation during the acute pharmacological effects may drive activity into specific or preferential networks, depending on the properties of the treatment. Thus different drugs may have different effects on a network level. This could explain why ECT has a wide profile of deleterious cognitive effects while isoflurane anesthesia or subanesthetic ketamine are less prone to producing negative cognitive effects. Since in ECT the electrical current led to the brain is in no way selective as to which neuronal populations are activated, this activity and remodeling of the networks may incite not only therapeutic effects but also changes that are detrimental to memory and cognitive functions.

6.5 The putative role of slow EEG activity in rapid antidepressant mechanisms

Our results provide evidence of a translationally relevant electrophysiological parameter – slow EEG activity – that correlates with specific phosphorylation alterations in neurotrophic pathways. The increase of slow EEG activity is particularly interesting, since similar increases in delta frequency power are physiologically evident during stages of non-rem (NREM) sleep (Davis et al., 2011). The SYNAPTIC HOMEOSTASIS HYPOTHESIS (SHY) proposed by GIULIO TONONI and CHIARA CIRELLI (2003) states that SWA, which increases as a function of previous wakefulness and decreases over the course of sleep, drives molecular and structural changes in neuronal networks during NREM sleep. While the task of connecting sleep- and waking-related molecular and cellular changes to behavioral and cognitive effects is unarguably complex, SHY provides an interesting framework to apply to the effects of rapid-acting antidepressants.

The SHY proposes that a net increase in the strength of neuronal connections takes place during waking, while a net decrease takes place during sleep (Tononi & Cirelli, 2014). Activity-induced changes during waking are encoded into long-lasting changes in the strength, number, and wiring of neuronal connections, driven by cellular signaling cascades. Among these cascades are activity- and plasticity-related genes such as *Bdnf* and *Arc* and the phosphorylation of transcription factors such as CREB. The expression of these LTP-related molecular markers is, however, markedly reduced during sleep (Cirelli & Tononi, 2000). While synaptic strengthening takes place during wakefulness and learning, a balancing act is required to prevent excess potentiation. According to SHY, this balance is achieved by the consecutive potentiation and depotentiation taking place along the 24-hour sleep/wake cycle in humans. During waking hours, our brains are active, and we connect to the external environment through our senses. This provides an optimal time for interacting and learning. During sleep, however, our brains become disconnected from the external world, allowing the restoration of synaptic weights to take place. This state is particularly ideal for systematic synaptic renormalization because it is not influenced by ongoing sensory experience and activity (Tononi & Cirelli, 2019). Notably, recent ultrastructural evidence from experiments using three-dimensional electron microscopy in mice demonstrated a decrease in the axon-spine interface after sleep compared with wakefulness (de Vivo et al., 2017). Moreover, other studies have reported decreases in cortical AMPAR expression after sleep (Diering et al., 2017; Vyazovskiy et al., 2008).

The state of wakefulness is inherently accompanied by LTP-like changes in the brain and the buildup of synaptic potentiation, and is supported by increases in the synaptic density and neuronal complexity of animals subjected to interventions like an enriched environment or whisker stimulation (Knott et al., 2002; Kolb et al., 1998; May-Britt et al., 1998; Tononi & Cirelli, 2014). The SHY postulates that this potentiation is connected to the homeostatic increase of SWA during subsequent periods of sleep, and is perhaps mediated by the buildup of LTP-related molecules. While the mechanisms of SWA increase are still unclear, the increase of SWA after extended wakefulness does not seem to be explained only by neuronal fatigue after sustained firing (Rodriguez et al., 2016). The SHY proposes that the amount of SWA is a direct reflection of the strength of corticocortical synapses and their potentiation (Tononi & Cirelli, 2003).

In NREM sleep, cortical and thalamic neurons oscillate between up and down states, characterized respectively by the tendency to fire or not (Tononi & Cirelli, 2019). This rhythmic activity can be measured as slow waves in cortical EEG and has been proposed to be important for sleep-dependent down-selection, along with electrical activity like hippocampal sharp waves/ripples (Norimoto et al., 2018). Accumulating evidence suggests that sleep-dependent renormalization of synaptic strength spares neuronal connections that are most active during sleep (Tononi & Cirelli, 2019). According to SHY, a process must exist for selective down-selection in order for sleep to promote learning and memory consolidation while also permitting the refinement of circuitries and forgetting (Tononi & Cirelli, 2014). Such protection from synaptic depression has been evaluated in computer simulations (Hashmi et al., 2013; Nere et al., 2013) and recently gained support from an in vivo study where urethane anesthesia was used to reproduce the up and down states of NREM sleep (González-Rueda et al., 2018). In this study, conventional rules of spike-timing-dependent synaptic plasticity applied when presynaptic afferents in the mouse barrel cortex were optogenetically stimulated during down states. However, stimulation during up states never led to increases in synaptic strength, which remained unchanged when presynaptic activation was coupled with postsynaptic activity and decreased when postsynaptic activity was coincidental. As proposed by the work of González-Rueda et al. (2018) and discussed by Tononi and Cirelli (2019), since neurons rarely fire during down states and up states last longer than down states during sleep, these mechanisms could explain the wide yet synapse-specific renormalization that is able to spare those connections that fire congruently. In other words, synapses adequately strengthened during wakefulness and learning would be resistant to synaptic depression.

Our results demonstrate the connection between increased slow EEG activity and the activation of neurotrophic pathways (II, III). If these bear any similarity to the neurobiological mechanisms of sleep or to what SHY proposes, the latter phase of regulation (i.e. slow EEG activity after the acute effects) or the increase of slow EEG activity during subsequent nights may be related to the downscaling of neuronal connections. On the other hand, the first phase of excitation that occurs during acute treatment may activate specific patterns of neuronal activity, which then result in specific connections being preferentially spared from synaptic downscaling. Applied to ketamine, these mechanisms could result in the acute potentiation of selected networks, resulting in the rapid onset of antidepressant action. This potentiation would then spare these connections in the down-selection during subsequent sleep and slow EEG activity, effectively upkeeping the relative potentiation of these connections and consolidation into functionally meaningful changes that manifest as a lasting reduction of depressive symptoms.

Indeed, the rapid-acting antidepressant effects of ketamine are most prominent 24 hours after the treatment, essentially after a night of sleep. This timescale suggests that endogenous mechanisms of sleep regulation may indeed interact with the pharmacological effects of ketamine and other putative rapid-acting antidepressants. Moreover, the antidepressant effects of ketamine typically wear off within several days or a few weeks, but can be restored by another dose of ketamine. Hypothetically, this loss of antidepressant effects could result from several consecutive periods of renormalization during subsequent nights of sleep, which eventually reset the relative potentiation of specific networks if no further stimulus (i.e. ketamine treatment) is applied. Notably, increased SWA has been reported during the night following ketamine treatments, and this has been proposed to predict the therapeutic efficacy of the treatment (Duncan, Sarasso, et al., 2013).

Synaptic strength is governed by the trafficking and insertion of AMPARs into the synaptic membrane and by their removal. Among proteins involved in these processes are Homer1a (Diering et al., 2017), Arc (Okuno, et al., 2012), GSK3β (Beurel et al., 2016), and MAPK (Zhu et al., 2002). Our results demonstrate changes in the expression of Homer1a and Arc after N_2O administration and the subsequent regulation of GSK3β and MAPK during increased slow EEG activity. Notably, Tononi and Cirelli (2019) speculate that the Ser9 phosphorylation of GSK3β could be involved in the mechanism of tagging synapses potentiated during wakefulness and their protection from down-selection. Since our studies have concentrated on whole tissue lysates, it is impossible to further evaluate the compartmentalization of said molecular changes. In this regard, further studies using enriched postsynaptic densities or synaptosomal

preparations may provide additional insights into these mechanisms. Taken together, these findings, combined with the vast amount of literature pointing towards the role of slow EEG oscillations in the therapeutic efficacy of ECT, highlight the possibility that rapid antidepressant effects may be intimately tied to the neurobiology of sleep and memory.

6.6 Dose-dependent effects of ketamine on TrkB-GSK3β signaling

In our third study, we investigated the dose-dependent effects of ketamine in the regulation of TrkB-GSK3β signaling. Notably, a recent study by Zanos et al. (2016) suggested that a metabolite of ketamine, *cis*-HNK, is responsible for ketamine's rapid antidepressant effects. Thus, we also investigated whether it is ketamine or its *cis*-HNK metabolite that drives changes in the molecular pathways implicated in ketamine's antidepressant-like effects (III). We found that higher doses of ketamine (100 mg/kg, IP) effectively regulated TrkB, GSK3β, and p70S6K phosphorylation, while subanesthetic doses (10 mg/kg, IP) did not. Furthermore, our EEG recordings provide further evidence for slow EEG oscillations coinciding with the previously mentioned phosphorylation changes. High doses of ketamine capable of increasing delta frequency power also activate TrkB signaling. Moreover, our results demonstrate that an anesthetic dose of 6,6-d_2-ketamine produces alterations in the previously mentioned pathways similar to those produced by ketamine, while *cis*-HNK failed to produce any acute effects on slow EEG activity or TrkB signaling.

These results are especially interesting in the context of preclinical and clinical ketamine research. Subanesthetic doses of ketamine (~0.5 mg/kg given over a 40-minute infusion) have been consistently used in clinical trials and have been reported to produce antidepressant effects. However, there is also active discussion in the literature about the relationship between the antidepressant responses and the psychoactive or dissociative symptoms elicited by higher but still subanesthetic doses (Lai et al., 2014; Loo et al., 2016; Luckenbaugh et al., 2014; Niciu et al., 2018; Sos et al., 2013; Xu et al., 2016). Interestingly, in a recent clinical trial, lower doses (0.1 and 0.2 mg/kg) were not found to produce clinically meaningful antidepressant effects, while higher doses (0.5 and 1.0 mg/kg) were effective (Fava et al., 2018). In the preclinical context, a dose of 10 mg/kg has been most commonly used in studies demonstrating antidepressant-like effects in rodents (Li et al., 2010; Zanos et al., 2016). However, studies thoroughly validating the basis for the selection of this dose and its translational relevance are lacking.

A recently published study implicates BDNF and mTOR signaling in the antidepressant-like effects of HNK (Fukumoto et al., 2018). The authors report that antidepressant actions of (2R,6R)-HNK can be blocked in mice using an antibody against BDNF. Moreover, the blockade of L-type VGCCs, TrkB, or mTOR signaling result in abolished antidepressant-like behavioral effects, suggesting activity-dependent BDNF release to play a key role in the effects of HNK. Notably, 30 mg/kg of (2R,6R)-HNK was required to produce effects equivalent to those of 10 mg/kg of ketamine in behavioral assays and in the phosphorylation of mTOR. Our study used a relatively high dose of 20 mg/kg of *cis*-HNK, and we could not detect any statistically significant differences in p70S6K phosphorylation, a target downstream of mTOR activation. While a higher dose of HNK may indeed produce similar phosphorylation alterations as ketamine, 10 mg/kg of ketamine does not metabolize into 30 mg/kg of (2R,6R)-HNK or to 20 mg/kg of *cis*-HNK. This discrepancy of using massive doses of HNK compared to small doses of ketamine does not support the idea that ketamine's effects are solely mediated by HNK. It is plausible that ketamine and the part metabolized to HNK may interact to produce additive molecular changes. However, in our study, we compared the effects of equivalent doses of ketamine and 6,6-d_2-ketamine and found their effects to be essentially similar. Furthermore, while Fukumoto et al. (2018) reported increased mTOR phosphorylation after 10 mg/kg of ketamine, we did not see any changes in the phosphorylation of p70S6K with the same dose. The discrepancy between these results remains to be clarified, but may be due to differences in sample processing, for example, the use of raw lysates versus synaptosomal fractions.

6.7 Translational remarks

A severe translational gap exists between preclinical and clinical experiments in the study of rapid-acting antidepressant effects, with several preclinically promising drug candidates having failed in clinical trials. One possible way to achieve better relevance for preclinical results would be to comprehensively compare the effects of rapid-acting antidepressants like ketamine on translationally relevant electrophysiological parameters of brain activity. However, several limitations are involved in techniques such as EEG and their interpretations for mice versus humans. Comprehensive EEG recordings combined with the study of brain drug pharmacokinetics in rodents would still provide important information on adjusting treatments to further match the clinical setting. Notably, ketamine is most often administered as IP or SC injections to rodents. Almost all clinical trials have employed an IV infusion. This discrepancy likely exists for the convenience of the researchers and due to the difficulty of IV administration in rodents. However, several methods such as infusion minipumps could be considered to combat these obstacles. From this perspective, nitrous oxide also provides a more promising translational option to study the effects of putative fast-acting antidepressants in rodents, since its administration and pharmacokinetic properties are relatively similar in humans.

Behavioral assays have dominated the field of depression research since the very first tests were developed along with the discovery of monoaminergic antidepressants. Some of these tests, such as FST, sometimes demonstrate a rapid amelioration of depressive symptoms after antidepressant administration. Notably, humans typically do not experience the rapid alleviation of depressive symptoms with traditional antidepressants, raising questions about the nature of these responses in rodents. Many animal models also use long-term mild stress to produce depression-like phenotypes, however, the depressive behavior is typically ameliorated by the removal of the stressor (Grippo et al., 2003). Major depressive disorder, in contrast, often persists when external causes are improved (Belmaker & Agam, 2008). While these animal models might be useful in finding new drugs that act on monoaminergic mechanisms, they might not be as valuable in the discovery of novel antidepressants with lesser-known mechanisms of action. Moreover, the ability of these models to distinguish rapid antidepressant effects requires further study. Since our understanding of the pathogenesis of depression and the mechanisms of antidepressants remains incomplete, we are also lacking in animal models that effectively represent human depression (Nestler et al., 2002).

Instead of relying heavily on animal models, our studies mostly approached rapid-acting antidepressants from the perspective of their neuro-

pharmacological and neurophysiological features. This provided the opportunity to find shared pharmacological targets and features of various drugs that have clinically relevant fast-acting antidepressant effects. A possible limitation of our work is the use of naïve animals, which requires the presupposition that naïve animals will display relevant biochemical and physiological responses when treated with drugs that have clinical relevance in treating depression. As demonstrated by the work in this thesis, this line of approach has great potential for future discoveries. For example, combining complementary methods like phosphoproteomics, metabolomics, and RNA sequencing with translationally relevant *in vivo* imaging or electrophysiological measurements may give further insights into common targets of rapid-acting treatments.

Our results highlight decades-old research on the mechanisms of ECT and raise further important questions about the connection between physiological brain states and the molecular mechanisms driving the rapid-acting antidepressant effects of ketamine. If the mechanisms of action of rapid-acting antidepressants are related to putative intrinsic neurobiological mechanisms such as the modulation of network plasticity during SWA, several considerations may be important for future research. Most importantly, in clinical practice, subanesthetic ketamine and ECT are most often delivered during the early morning or early afternoon (C. Zarate & K. Järventausta, personal communications, 23.11.2018). In preclinical research, treatments are often given during the daytime, but since most rodent species (mice and rats) are nocturnal animals, the treatments take place during their inactive period. While the contrast between periods of activity and wakefulness are not as clearly defined in rodents as in humans, rodents are clearly much more active during the night. Pharmacological and behavioral tests conducted during the inactive period of animals, when sleep pressure is high, may have severe confounding effects for molecular and behavioral tests. This discrepancy between basic and clinical research may also contribute to why so many preclinically effective treatments of depression fail in clinical trials. Moreover, since human cortical excitability is also regulated in a circadian manner (Ly et al., 2016), understanding its implications for central nervous system disorders may provide ways to further advance human therapeutics.

Emerging evidence of the rapid antidepressant effects of psychedelic drugs may be ultimately important for unraveling the neurobiological mechanisms of ketamine as well. For example, psilocybin has also been suggested to produce changes in spontaneous cortical excitability (Kometer et al., 2013) and to increase global cerebral metabolic rate of glucose utilization (CMR_{glu}), with particular changes in the prefrontal cortex, associated limbic areas, and thalamus (Vollenweider, Leenders, Scharfetter, Maguire, et al., 1997). Essentially

similar increases in CMR_{glu} have been noted in patients receiving psilocybin and ketamine, and this has been proposed to support the idea of converging mechanism behind these different drugs (Vollenweider, Leenders, Scharfetter, Antonini, et al., 1997; Vollenweider & Kometer, 2010). Indeed, several studies have demonstrated that activation of the $5HT_{2A}$ receptor increases excitatory activity in the PFC (Aghajanian & Marek, 1999; Beique et al., 2007; Puig, 2003). Moreover, psychedelic drugs have also been shown to increase cortical glutamate release in rodents (Muschamp et al., 2004; Scruggs et al., 2003), similar to subanesthetic ketamine (Chowdhury et al., 2017; Moghaddam et al., 1997). Thus, it is tempting to speculate that psychedelics may also evoke similar molecular alterations after their acute effects.

To further advance the mechanistic knowledge of rapid-acting antidepressant treatments, it is also worth considering the psychological dimensions of using psychotropic drugs as treatments. Biochemistry aside, the dissociative states produced by ketamine and N_2O bear some resemblance to the psychedelic states induced by drugs like psilocybin. Both ketamine and psychedelics have been suggested to have positive psychological effects for depression and anxiety in patients that are receiving end-of-life care (Gasser et al., 2015; Griffiths et al., 2016; Grob et al., 2011; Iglewicz et al., 2015; Sexton et al., 2018; Stefanczyk-Sapieha et al., 2008; Zanicotti et al., 2013). The subjective psychological experience triggered by potent psychotropic drugs has not received much attention in relation to the effects of anesthetic drugs, though it is one of the key interests in the study of psychedelic drugs. The role of "set and setting", representing the psychological state and the environment in which psychedelic therapy takes place, has been given special attention in modern clinical studies of psychedelic drugs (Carhart-Harris et al., 2018; Johnson et al., 2008). If rapid-acting antidepressant effects are related to the modulation of neuronal plasticity and memory formation, the role of well-designed psychotherapy may be crucial in supporting their therapeutic effects. Indeed, accumulating evidence suggests that traditional antidepressants may work better in a favorable environment, while a stressful environment promotes worse outcomes (Alboni et al., 2017; Branchi et al., 2013; Chiarotti et al., 2017; Viglione et al., 2019). It remains to be investigated whether psychological and environmental factors also contribute to responses in patients receiving ketamine and other putative rapid-acting antidepressant treatments.

7 CONCLUSIONS

In this thesis, we examined the phosphoproteomic effects of brief isoflurane anesthesia in the mouse hippocampus and studied several molecular and electrophysiological changes induced by fast-acting antidepressants. The phosphoproteomic study demonstrates that isoflurane produces broad alterations in the hippocampal phosphoproteome, and that several molecular alterations are similarly regulated by anesthetic drugs other than isoflurane. Most importantly, our results highlight decades old research implicating the association of post-ictal slow EEG activity with the therapeutic effects of ECT and demonstrate that rapid-acting antidepressant treatments like nitrous oxide and ketamine may share similar features of cortical excitation and inhibition. Moreover, we demonstrate that nitrous oxide regulates the activity of TrkB, GSK3β, p70S6K, and MAPK differentially during acute drug exposure and the subsequent withdrawal, and that ketamine dose-dependently regulates these signaling pathways without the direct influence of its metabolite HNK. Based on these studies, we formulated a hypothesis of the two phases of rapid antidepressant action and highlighted the intriguing association of slow EEG activity and the activation of signaling pathways implicated in rapid antidepressant effects, which may be related to the complex neurobiological mechanisms of sleep and memory. Further studies will be instrumental in understanding the functional significance of the molecular alterations associated with the described phenomena.

The main conclusions are:

I brief isoflurane anesthesia produces prominent phosphoproteomic changes in the mouse hippocampus;

II anesthetic/sedative doses of isoflurane, sevoflurane, ketamine, and urethane produce similar phosphorylation alterations on GSK3β, MAP2, and p44/42-MAPK;

III nitrous oxide produces molecular changes indicative of cortical excitation and evokes the emergence of homeostatic slow EEG oscillations after the cessation of gas flow, during which TrkB-GSK3β phorylation is upregulated;

IV the emergence of post-treatment slow EEG oscillations is a shared feature of nitrous oxide, subanesthetic ketamine, and flurothyl;

V medetomidine sedation increases slow EEG oscillations and induces the phosphorylation of TrkB-GSK3β, but does not produce antidepressant-like effects in mice;

VI anesthetic doses of ketamine regulate the phosphorylation of TrkB-GSK3β most prominently; and

VII increased phosphorylation of TrkB-GSK3β is not solely dependent on ketamine's non-sedative metabolite *cis*-hydroxynorketamine.

Acknowledgements

THE WORK leading to this thesis was carried out at the University of Helsinki in several institutes: the Neuroscience Center during 2015 and 2016, the Department of Physiology and Neuroscience, Faculty of Biological and Environmental Sciences during the years 2016 through 2018, the Department of Pharmacology and Pharmacotherapy, Faculty of Pharmacy, and the SleepWell Research Program, Faculty of Medicine during the years 2018 and 2019. Some of the studies were done in close collaboration with the Turku Center for Biotechnology at the University of Turku and the Institute of Biomedicine at the University of Helsinki.

First and foremost, I would like to express my deep respect and gratitude for Associate Professor Tomi Rantamäki, who has been the guiding force of my scientific career. Our paths crossed during my master's studies, where I was struck by the exciting atmosphere of Tomi's lecture about neurotrophic factors and TrkB. I followed his Trk's and stumbled down the rabbit hole into the peculiar world of neuroscience. Tomi helped me thrive in this new habitat. Not only did he share his knowledge, but he also brought up controversies and fought stale truths. Inspired by his enthusiasm, I was ready to take the red pill: to embark on a quest for knowledge in the face of uncertainty. That is exactly what happened, when Tomi received funding to start his own group and I happened to be in the right place at the right time. From there onwards, I had the amazing opportunity to work on my PhD while starting up the Laboratory of Neurotherapeutics along with Tomi, one reagent and experiment at a time. In retrospect, a lot of money was spent pursuing crazy ideas that would never see the light of day. However, not all was in vain, as can be witnessed by this thesis. I cannot stress how privileged I have been to have Tomi as my supervisor and colleague. He is not only a hard-working scientist, but also an excellent leader. These qualities were best witnessed when we had four people working in his tiny office due to limited space. There we existed in harmony, broken only by bouts of lively laughter and bad jokes. We worked long days and kept sending emails late into the night while the stars crept up in the sky. Most importantly, we shared and reveled in the excitement of science.

Second, I would like to express my very great appreciation for all the opportunities I have had to grow as a student by learning from good teachers. In the Faculty of Pharmacy, I consider Professor Raimo Tuominen to be one of the best. Besides acting as my thesis committee member, I had the pleasure to learn from his vast knowledge in pharmacology during my earlier studies. Most importantly, Raimo has been very supportive, easy to approach, and always ready to give advice to students. I am deeply grateful for his continued

support throughout these years. I would also like to express my very great appreciation to all my mentors over the past years. I am particularly grateful for the assistance of Dr. Henri Autio and Dr. Hanna Antila. Henri guided me through my first practical lab work and Hanna continued to give important advice throughout my work. They both made a lasting impression with their flawless professionalism and witty puns. Their attitude, curiosity, and intelligence contributed to my decision to continue to work towards a PhD. They also taught me the sacred art of western blotting, a delicate yet prestigious ritual that can be refined only by years of repetition.

I wish to thank Professor Claudio Rivera and Adjunct Professor Henri Huttunen for acting in my thesis committee and for all the helpful discussions during our meetings. I would like to say thanks to Adjunct Professors Petri Hyytiä and Jouni Sirviö for acting as reviewers of this thesis, and to Professor Ronald Duman for accepting the invitation to act as my thesis opponent. I also want to thank Outi Nikkilä for her technical assistance, Katri Wegelius for her work in coordinating the PhD studies and all the wonderful personnel of the Biocenter 3 animal facilities for making my work so much easier.

My sincere thanks belong to all the past and present colleagues with whom I have had the pleasure to work and spend time. You have given me help and advice numerous times. I would particularly like to say thank you to Wiebke, Marko, Salla, Stanislav and Nobuaki. Special thanks are deserved by Okko for all the stimulating discussions and artistic endeavors! I would also like to acknowledge the important role of all the co-authors and collaborators in my thesis publications. Science is essentially team work.

My special thanks are extended to all my friends who have supported my progress throughout the years. During my pharmacy studies, I have been privileged to meet exceptional people and to make amazing new friends, of whom I would especially like to thank Mr. Palm, Mr. Lindholm, and Mr. Teppo.

In the end, I owe my deepest gratitude to my parents, Kaarina and Henrik, whose continuous support, commitment, and love have encouraged me to push forward in life, and to my beloved Piia, who not only encouraged my decision to pursue a PhD, but also supported me throughout the long and arduous journey.

The Academy of Finland, Business Finland, Doctoral Programme Brain & Mind, the Orion Research Foundation, the Finnish Pharmaceutical Society, the Finnish Pharmacists' Society, the Finnish Pharmacological Society, and The Association of Pharmacy Teachers and Researchers are thanked for their very important financial support.

Helsinki, March 2019

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